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Therapeutic Strategies for Alzheimer's Disease

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Abstract Therapeutic approaches for Alzheimer's disease (AD) are guided by four disease characteristics: amyloid plaques, neurofibrillar tangles (NFT), neurodegeneration, and dementia. Amyloid plaques are composed largely of 4 kDa β-amyloid (Aβ) peptides, with the more amyloidogenic, 42 amino acid form (Aβ42) as the primary species. Because multiple, rare mutations that cause early-onset, familial AD lead to increased production or aggregation of Aβ42, amyloid therapeutics aim to reduce the amount of toxic Aβ42 aggregates. Amyloid-based therapies include γ-secretase inhibitors and modulators, BACE inhibitors, aggregation blockers, catabolism inducers, and anti-Aβ biologics. Tangles are composed of paired helical filaments of hyperphosphorylated tau protein. Tau-based therapeutics include kinase inhibitors, microtubule stabilizers, and catabolism inducers. Therapeutic strategies for neurodegeneration target multiple mechanisms, including excitotoxicity, mitochondrial dysfunction, oxidative damage, and inflammation or stimulation of neuronal viability. Although not disease modifying, cognition enhancers are important to treat the symptom of dementia. Strategies for cognition enhancement include cholinesterase inhibitors, and other approaches to enhance the signaling of cholinergic and glutamatergic neurons. In summary, plaques, tangles, neurodegeneration and dementia guide the development of multiple therapeutic approaches for AD and are the subject of this review.

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Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting an estimated 27 million people worldwide in 2006 [1]. Age is the greatest known risk factor for AD with an incidence of 25–50% in people aged 85 years or older [2]. As the average age of the population increases, the number of patients with AD is expected to rise exponentially. AD is the fifth leading cause of death in people aged 65 and older, and most patients eventually need nursing home care. Consequently, AD has a large economic impact with estimated direct and indirect costs of $148 billion dollars annually for 2005 in the US [3]. In addition to these economic costs, AD causes significant distress and suffering to patients and family members.

Patients are diagnosed with probable AD based on the presence of dementia with progressive worsening of memory and other cognitive functions and with the exclusion of other causes of dementia. The diagnosis can only be confirmed post mortem based on several neuropathologies, including extracellular plaques, intracellular tangles, and neurodegeneration [4]. Dementia is a required part of the diagnosis [5] since plaques and tangles are also observed in cognitively normal adults, although usually to a lesser extent [6, 7]. Two classes of medications, cholinesterase inhibitors and an *N*-methyl-D aspartate (NMDA) antagonist, are currently approved for AD. Although these therapeutics show some clinical benefit, many patients do not respond, and these drugs do not modify disease progression [2, 8]. For these reasons, identification of

additional therapeutics for this devastating disease is a major focus of the pharmaceutical industry. These new therapeutics are aimed at the four AD characteristics: plaques, tangles, neurodegeneration, and dementia.

β-Amyloid-Based Therapeutics

Plaques are comprised primarily of β-amyloid (Aβ) peptides that are formed by the sequential cleavage of the amyloid precursor protein (APP; Fig. 1). APP is first cleaved by the β-site APP-cleaving enzyme (BACE), an aspartyl protease, to form the N-terminus of Aβ. The resulting C-terminal fragment of APP is then cleaved at multiple sites by γ-secretase to form Aβ isoforms ranging from 37 (Aβ37) to 43 (Aβ43) residues. γ-Secretase is a protein complex that includes nicastrin, Aph-1, Pen-2, and either presenilin-1 (PS-1) or presenilin-2 (PS-2) [9].

Aβ42 is most closely linked with AD pathogenesis even though Aβ40 is the most abundant Aβ species synthesized. Mutations in the APP, PS-1, and PS-2 genes that lead to rare, familial forms of AD implicate Aβ42 as the primary toxic species [10]. In particular, the Swedish mutation in APP increases BACE1 cleavage and, as a result, increases all Aβ species. The London mutation in APP, as well as mutations in PS-1 and PS-2, preferentially increase the production of Aβ42 leading to an increased Aβ42/Aβ40 ratio and thereby increased levels of Aβ oligomers. Finally, the Arctic mutation in APP increases the aggregation rate of Aβ and also the level of Aβ oligomers. Consistent with this phenotypic analysis, preclinical models show that APP overexpression in mice leads to plaques and cognitive deficits. The most prominent form of Aβ in AD brain is fibrillar Aβ42 in plaques, and although this form of Aβ is not believed to be the major cause of disease, it likely contributes to the disruption of normal neuronal function [11, 12]. Current evidence suggests that soluble Aβ42, potentially including oligomeric, protofibrillar, and intracellular Aβ42, plays the most significant role in the disease process [13–15]. Oligomeric Aβ inhibits long-term potentiation [16, 17] and memory when injected into rats [14]. In addition, oligomeric Aβ levels correlate with memory deficits in transgenic mice [18, 19] and a small molecule that reduces oligomer levels reverses cognitive deficits in transgenic mice [20]. Taken together, the amyloid pathology, human genetics of familial AD, and preclinical studies support the amyloid hypothesis and suggest multiple Aβ-based therapeutics (Fig. 1).

γ-Secretase inhibitors can reduce Aβ synthesis and thereby prevent Aβ aggregation and reverse APP-induced cognitive deficits in preclinical models [21]. Unfortunately, γ-secretase cleaves transmembrane proteins in addition to APP [22]. While the physiologic role of γ-secretase cleavage for most of these substrates is unknown, γ-secretase cleavage of the Notch family of transmembrane receptors is required for Notch signaling. As a result of the inhibition of Notch signaling, chronic dosing of γ-secretase inhibitors causes changes in the gastrointestinal tract, spleen, and thymus that limit the extent of Aβ inhibition attainable in vivo [23–25]. Despite this limitation, γ-secretase inhibitors can improve cognitive deficits at tolerable doses in preclinical models [26]. Based on these findings, γ-secretase inhibitors, including LY-450139 (Lilly) [27, 28] and MK0752 (Merck) [29], are being tested in humans.

The identification of BACE1 as the enzyme required for brain Aβ formation was met with great enthusiasm, particularly when the original analysis of BACE1 knockout mice did not reveal any undesired phenotypes [30]. In addition, BACE1 knockout mice have almost complete reductions in brain Aβ [31]. This initial enthusiasm has, however, been dampened by two issues. First, several investigators have identified other phenotypes in the BACE1 knockouts, including cognitive deficits [32–34], premature death [35], and hypomyelination [36, 37]. This observed hypomyelination results from a reduction in neuregulin-1 processing, although recent studies have shown no detrimental effects of BACE inhibitors on neuregulin-1 cleavage after 1 week of treatment with a BACE inhibitor [38]. Second, it has been difficult to design potent, brain penetrant BACE1 inhibitors. Efflux by the P-glycoprotein transporter appears to be one problem associated with this class of inhibitors [39, 40].

Small-molecules that shift Aβ42 to shorter Aβ species, such as Aβ37 and Aβ38, were discovered while investigating the mechanism for the reduced prevalence of AD among users of nonsteroidal anti-inflammatories (NSAIDs)

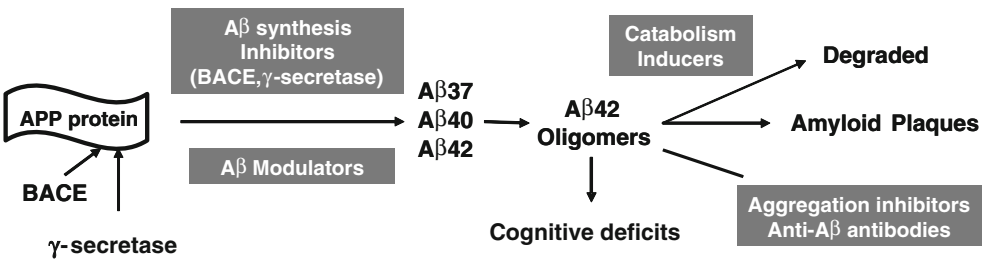

Fig. 1 The formation of Aβ by cleavage of APP and its conversion to Aβ oligomers and amyloid plaques is shown. Potential therapeutic approaches to decrease Aβ toxicity are indicated in the *shaded boxes*

[41]. Subsequent studies have shown that certain NSAIDs modulate Aβ synthesis due to binding to γ-secretase [42] and not because of cyclooxygenase inhibition. Despite binding to γ-secretase, Aβ modulators do not cause Notch toxicities [43]. The most advanced γ-secretase modulator, *R*-flurbiprofen (Myriad), is in phase III clinical trials [44]. Unlike *S*-flurbiprofen, *R*-flurbiprofen does not inhibit cyclooxygenase and, consequently, does not cause the gastrointestinal side effects due to cyclooxygenase inhibition. Other modulators have been reported by several groups [45].

Several Aβ aggregation inhibitors have been discovered. 3-Amino-1-propanesulfonic acid (3APS; Neurochem) was identified based on the observation that glycosaminoglycans stimulate Aβ aggregation. 3APS binds monomeric Aβ, decreases Aβ deposition in transgenic mice [46], and reduces CSF Aβ in humans [47]. 3APS is in phase III trials [48]. An essential role for metals, particularly copper and zinc, in Aβ aggregation [49] led to the discovery of small molecule chelators that perturb Aβ-metal binding. Clioquinol (Prana), an antibiotic, partially dissolved plaques in vitro and prevented plaque deposition in transgenic mice [50]. Clinical trials were halted due to an impurity but provided some evidence for reduced plasma Aβ and improved cognition [51, 52]. A second generation chelating agent (PBT2) is in phase II [48]. Scyllo-inositol was identified based on the observation that phosphatidylinositol stimulates Aβ aggregation. Scyllo-inositol binds an Aβ oligomer to inhibit further aggregation and toxicity [53] and reduces plaque deposition and cognitive deficits in a transgenic mouse model [54]. Scyllo-inositol is in Ph II clinical trials (Transition Therapeutics/Elan). A variety of other molecules that prevent Aβ aggregation have also been identified [55]. One potential issue for aggregation inhibitors is a shift in the equilibrium between the less toxic aggregated forms to more toxic soluble intermediates, such as protofibrils [56].

Methods to stimulate Aβ degradation are an additional approach to decrease Aβ oligomers [57, 58]. For example, somatostatin [59] and PAI-1 inhibitors can indirectly increase neprilysin and plasmin activity, respectively, which leads to increased degradation of Aβ.

Active vaccination with AN1792 (Elan/Wyeth), which contains Aβ42 aggregates, was first tested in humans based on impressive preclinical studies [60]. Unfortunately, meningo-encephalitis in 6% of the vaccinated patients caused the termination of these studies [61]. The encephalitis is hypothesized to result from T-cell activation based on examination of post mortem tissue [62–64] and studies in mice [65]. Further evaluation of antibody responders to AN1792 treatment showed cognitive improvement in a composite score for the neuropsychological test battery, but not in the ADAS-cog (AD assessment scale-cognitive subscale) [66]. Analysis of a subset of responders showed reductions in CSF tau [66] and evidence for plaque clearance, but no changes in cerebral arterial amyloid or neurofibrillary tangles [62–64]. Paradoxically, antibody responders had a greater brain volume decrease than placebo patients based on magnetic resonance imaging measurements [67]. Based on these positive clinical trends, second-generation vaccines that are designed to avoid the encephalitis observed with AN1792 are entering clinical development.

The positive findings with Aβ42 immunization in mice led to similar studies using passive immunization with anti-Aβ antibodies. These studies in transgenic mice showed that peripherally administered antibodies could reduce plaque burden [68] and reverse cognitive deficits [69]. Several mechanisms have been proposed to explain these results, including binding to Aβ monomers to prevent oligomerization, binding to Aβ oligomers to increase clearance or prevent toxicity, recruitment of immune effector cells, such as microglia, to remove fibrillar Aβ, and efflux of brain Aβ into peripheral compartments due to a shift in the equilibrium between brain Aβ and plasma Aβ [58]. The antibody epitope on Aβ can affect which Aβ forms (monomeric, oligomeric, and fibrillar) are bound, and the antibody constant region can affect which neutralization mechanisms are possible [70]. While passive immunization will likely avoid the encephalitis observed with active immunization, microhemorrhaging and increased vascular amyloid has been observed in transgenic mice [71–73]. Although the mechanism responsible for the increased vascular amyloid and microhemorrhages is unknown [74], anti-Aβ antibodies that do not bind vascular amyloid [72] and deglycosylated antibodies [75] have a reduced frequency of these potential problems in transgenic mice. Bapineuzumab (Elan/Wyeth) binds the N-terminal region of Aβ and, consequently, is likely to recognize monomeric, oligomeric, and fibrillar Aβ, including vascular amyloid. Bapineuzumab is completing phase II trials [58] and is scheduled to begin Ph III studies in 2008. LY-2062430 (Lilly), a humanized version of anti-Aβ antibody 266, is in Ph II studies [58]. Antibody 266 binds monomeric Aβ, but not fibrillar Aβ, and does not cause microhemorrhaging in transgenic mice [72]. Other anti-Aβ antibodies and non-antibody biologics that bind Aβ are likely to enter clinical trials this year.

Tau-Based Therapeutics

Hyperphosphorylated, conformationally altered tau proteins form the paired helical filaments that compose intracellular tangles in AD brain. Tau is a 50- to 75-kDa protein with six different splice variants [76]. Tau binds and stabilizes microtubules, while hyperphosphorylated tau from AD brain disrupts microtubule structure [77]. The presence of

tangles in AD and their correlation with cognitive status suggests an important role for abnormal tau in dementia (reviewed in [76]). Although no mutations in the tau gene have been associated with AD, a number of tau mutations are associated with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), a neurodegenerative disease with tangles but without amyloid plaques [78]. FTDP-17 and other tauopathies, such as progressive supranuclear palsey, Pick's disease, and agyrophilic grain disease, demonstrate that tau abnormalities are sufficient to cause neurodegenerative disease (Fig. 2).

A growing body of literature demonstrates Aβ exacerbation of tau abnormalities, suggesting that tau is downstream of Aβ-mediated effects in AD [79]. When tau transgenic mice are crossed with APP transgenic mice, there is an enhancement in tau abnormalities, but not Aβ pathology [80, 81]. Likewise, intracerebral injection of Aβ increases tau pathology, including in distant regions with projections to the injection site [82, 81]. Furthermore, Aβ oligomers increase tau phosphorylation in cultured cells [83], and anti-Aβ oligomer antibodies reduce inappropriate tau accumulation in neurons of triple transgenic mice [84]. Finally, knockout of the murine tau gene in an APP transgenic line prevents the cognitive deficits presumably caused by Aβ oligomers [85]. The mechanism by which tau loss suppresses Aβ-induced deficits is unclear because tau abnormalities, including hyperphosphorylation, were not detected in the parent line.

Although tangles are a pathologic feature of AD brains, several lines of evidence suggest that tangles are neuroprotective rather than neurotoxic [86], as was hypothesized for plaques. Based on examination of human brains, neurons are believed to function with neurofibrillary tangles for decades [87]. hTau transgenic mice have tangles and severe neurodegeneration, but the neurons with tangles do not show selective signs of distress and are too few in number to account for the dramatic loss in neurons observed in this model [88]. Tg4510, an inducible tau transgenic line, shows dramatic and rapid tangle formation, neurodegeneration, and behavioral deficits when tau-P301L is expressed [89]. When tau-P301L is repressed, neurodegeneration and cognitive deficits, but not tangles, are greatly reduced. Further studies using these mice report that tau multimers correlate with cognitive deficits. Similar multimers are also observed in FTDP-17 and AD brain tissue [90] and may be related to the granular tau oligomers observed by atomic force microscopy in extracts of AD brain tissue [91]. Agents that inhibit tau fibrillization have been identified using in vitro assays [92], and it will be interesting to see these agents used in tau transgenic mice.

Reducing tau phosphorylation via inhibition of kinases is a major therapeutic strategy based on the presence of hyperphosphorylated tau in AD brain [93, 94]. Unfortunately, this effort is complicated by the large number of tau phosphorylation sites, the unknown role of individual phosphorylation sites in disease etiology, and the ability of multiple kinases to phosphorylate individual sites [95]. Despite these complications, glycogen synthase kinase 3 (GSK3) has emerged as an interesting therapeutic target. The serine/threonine kinase GSK3 can phosphorylate many tau epitopes that are increased in AD, and activated forms of GSK3 are concentrated in dystrophic neurites and neurons with pretangle and tangle pathology [95]. GSK3 overexpression in FTDP-17 mutant tau transgenic mice [96] and *Drosophila* [97] enhances tau hyperphosphorylation, fibrillization, and neurodegeneration. Furthermore, toxic

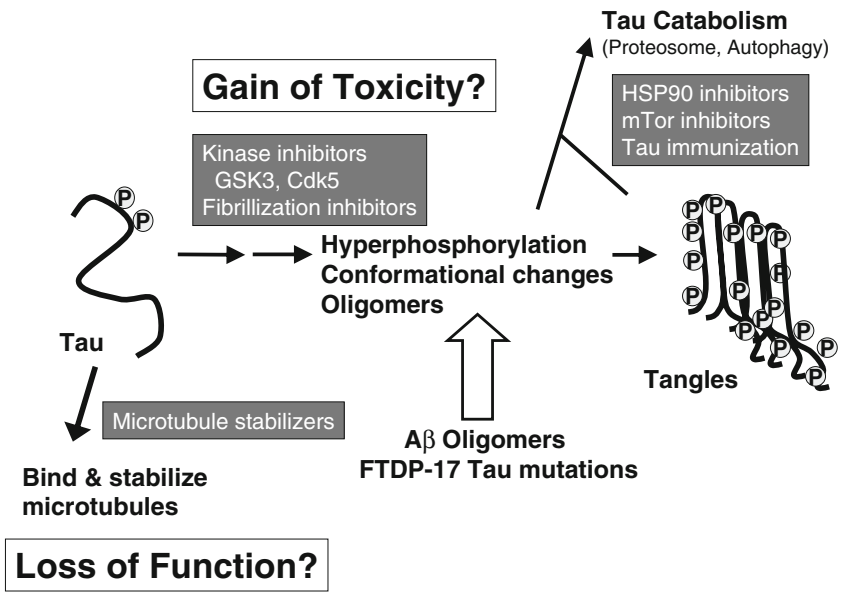

Fig. 2 Tau-based therapeutic approaches to AD focus on methods to compensate for a loss of tau function (microtubule stabilization) or to prevent/remove potentially toxic forms of tau. Although it is not yet clear which form of tau is toxic in neurons, significant evidence suggests that tangles are not a pathogenic species

forms of Aβ activate GSK3 [95], while neuroprotective Aβ oligomer antibodies reduce GSK3-mediated tau phosphorylation in vivo and in vitro [98]. Lithium, currently used therapeutically for bipolar disorder, and other GSK3 inhibitors reduce tau pathology and neurodegeneration in tau transgenic mice [99, 100]. Interestingly, inhibition of GSK3 in APP transgenic mice using lithium or expression of a dominant-negative GSK3 reverses cognitive deficits and reduces Aβ42 and phospho-tau [101]. In addition, GSK3 inhibitors may reduce Aβ and inflammation which could also benefit AD patients [101, 102]. Recent data also suggests GSK3 inhibition plays a significant role in synaptic plasticity, which may be involved in learning and memory. GSK3 inhibition suppresses long-term depression (LTD) and stimulates or consolidates long-term potentiation (LTP) [103, 104]. GSK3 is an important kinase in many pathways, including regulation of the β-catenin pathway involved in cell proliferation and growth. In fact, β-catenin activation may underlie the neuroprotective [105, 106] and antidepressant activities [102] of lithium. A note of caution for this target is the association of increased β-catenin activity with colon and other forms of cancer [106]. Even so, GSK3 inhibition may be beneficial for other types of cancer [107–109], and lithium usage does not increase cancer risk in bipolar disorder patients [102]. Many small molecule GSK3 inhibitors have been developed [93, 110, 111]. Neuropharma is in phase I clinical trials with a GSK3 inhibitor for AD [112, 113]. Lithium is also in a National Institute on Aging (NIA)-funded clinical trial for AD [114].

Cyclin-dependent kinase 5 (Cdk5) has also been implicated in tau hyperphosphorylation [93]. Cdk5 requires an accessory protein, usually p35 or p39, for activity. Calpain cleavage of p35 and p39 creates the more stable p25 and p29 forms. Both Cdk5 specific activity and p25 levels are reported to be increased in AD brain, but this finding is controversial [95]. Co-expression of Cdk5 and p35 increases tau-mediated toxicity in *Drosophila* [115]. Some transgenic p25 mouse lines hyperphosphorylate tau, but they do not form fibrils [116, 117]. Cdk5 can decrease GSK3 activity in an age-dependant manner, as observed in both p25 transgenice and p35 null mice [118–120]. This complex interplay between Cdk5 and GSK3 activities reduces the pTau lowering effects expected for a Cdk5 inhibitor in vivo [120]. Cdk5 conditional knockdown mice show enhanced learning and memory and a decreased threshold for LTP [121], and Cdk5 inhibition reduces Aβ production in vivo [120], suggesting possible beneficial effects of inhibitors beyond tau phosphorylation. Cdk5 inhibitors are in preclinical development [93, 94, 122].

Other kinases may also play a role in tau hyperphosphorylation, including microtubule affinity regulating kinases, protein kinase A, casein kinase, and the mitogen-activated protein kinase family (ERK1, ERK2, JNK, and p38 kinases) [93–95]. Preclinical development is ongoing for most of these targets. K252a is a nonselective kinase inhibitor that inhibits ERK-2, Cdc2, GSK3β, PKA, and PKC. K252a reduces motor deficits and a 64-kDa hyperphosphorylated tau species without affecting tangle formation in an FTDP-17 tau transgenic model [123]. Activation of tau phosphatases is also an attractive target, but this effort is hampered by the lack of a clear target for pharmacological manipulation [93].

Reductions in tau levels and increased catabolism of abnormal forms of tau are also therapeutic strategies for AD. Hsp90 inhibitors were identified in a cellular screen for small molecules that decrease total tau levels [124]. The multimeric Hsp90 complex helps to refold, stabilize, or facilitate ubiquitination and proteosomal degradation of abnormal cellular proteins. Hsp90 inhibitors, which bind the ATP-binding site on Hsp90 and inhibit its ATPase activity, stimulate the degradation of Hsp90 client proteins. The Hsp90 inhibitors PU-DZ8 and EC102 reduce phospho-tau, but not total Tau, in two tauopathy models [125, 126]. Hsp90 inhibitors may also reduce phospho-tau indirectly by increasing the degradation of the Cdk5 activator, p35 [126]. Hsp90 inhibitors are also being developed for oncology indications where some undesired side effects have been observed. A useful therapeutic window for Hsp90 inhibitors in AD may be possible because EC102 binds with higher affinity to AD brain tissue from affected areas [125]. In a separate approach, a recent screen identified nine compounds with the ability to selectively reduce tau mRNA [127]. Finally, tau immunization may also be a viable approach even though tau is an intracellular protein [128].

Stimulation of autophagy is an additional approach to remove tau aggregates [129]. Autophagy is a highly regulated system of vesicle formation where cytosolic contents are encapsulated by vesicles that eventually fuse with lysosomes for degradation. A role for autophagy in AD is suggested by its upregulation in AD brain and the increased concentration of autophagic vesicles in dystrophic neurites surrounding plaques [130]. Autophagy can be stimulated by inhibitors of the mammalian target of rapamycin (mTOR) kinase. Potential issues with mTOR inhibitors include immunosuppression [132], autophagic cell death [131], and increased Aβ production since autophagic vesicles produce Aβ [130]. mTOR inhibitors, as well as other approaches to stimulate autophagy, are in preclinical testing [131, 132].

Tau abnormalities in AD may also cause neurotoxicity by a loss of function mechanism. Tau binding to microtubules is a dynamic process normally regulated by phosphorylation. Tau hyperphosphorylation and aggregation would be expected to reduce binding to microtubules and thereby stability. Microtubule stabilizing agents protect cultured neurons from Aβ42, chloroquine, and glutamate-

induced toxicity [133–135]. Paclitaxel (Angiotech Pharmaceuticals) reversed deficits in fast axonal transport, increased microtubule numbers, and improved motor deficits in transgenic mice with tauopathy in the spinal cord [136]. Because of poor brain penetrance, paclitaxel is unlikely to be suitable for AD. Interestingly, there were no changes in the accumulation of fibrillar tau in spheroids. When microtubule stabilizing agents are used for chemotherapy, a major side effect is peripheral neuropathy [137]. Neuropathy may not be an issue for AD because the doses required for benefits in tauopathy models are lower than those used for cancer [138]. In addition to traditional microtubule stabilizing compounds, the eight amino acid peptide NAP (AL-108, Allon Therapeutics) may also work as a microtubule stabilizer, although it is also reported to reduce Aβ aggregation [139]. Chronic treatment with NAP reduces hyperphosphorylated, insoluble tau and behavioral deficits in a tau and APP transgenic mouse line [140]. AL-108 is in phase II clinical trials [139].

Approaches to Inhibit Neurodegeneration

A loss of gray matter, particularly in the hippocampus, cholinergic basal forebrain, and entorhinal cortex, characterizes AD [141]. Although initial studies suggested neuronal loss, a more careful examination suggests that a considerable amount of parenchymal loss is due to neuronal shrinkage and synapse loss [4, 141, 142] (Fig. 3). For this reason, stimulation of existing neurons may be beneficial in AD. NGF and BNDF are reduced in AD brain and may be useful to stimulate hypofunctional neurons [143]. Further support for NGF therapeutics comes from the analysis of mice which express a neutralizing antibody to NGF and, consequently, display age-dependent loss of cholinergic neurons, cognitive deficits, plaques, and tangles [144]. Therapeutic use of growth factors has been disappointing, with side effects such as pain and inappropriate fiber sprouting [145]. Approaches to express NGF in the basal ganglia by surgical implantation of fibroblasts or viral vectors expressing NGF appear more promising and are in clinical trials [146]. Neurotrophins bind to two types of receptors; the trk receptors stimulate neuronal survival, while the p75NTR and sortilin receptors can activate cell death pathways. As a result, both trk receptor agonists and p75NTR antagonists are in preclinical stages of development [147, 148].

Insulin and insulin like growth factor (IGF) are also neurotrophic, and type 2 diabetes is a risk factor for AD [143, 149]. Paradoxically, transport of insulin into the brain is reduced during hyperinsulinemia and diabetes. Acute insulin administration in normal subjects and AD patients results in an enhancement of cognitive function. Furthermore, brain tissue from diabetic rats show abnormalities in both Aβ and tau pathways, and the presence of dystrophic neurites [150]. For these reasons, anti-diabetic therapies are also being tested for AD including phase III clinical trials of the peroxisome proliferator-activated receptor-γ (PPARγ) agonist rosiglitizone [151].

There are several forms of neurotoxicity which are hypothesized to be involved in the etiology of AD: inflammation, oxidative stress, mitochondrial dysfunction, calcium dysregulation and excitotoxicity. A role for neuroinflammation in AD is suggested by the observation of activated inflammatory markers on microglia, astrocytes, and neurons near plaques, the ability of Aβ to bind and activate microglia, and the reduced incidence of AD with NSAID usage [152]. Neurotoxicity may result from this

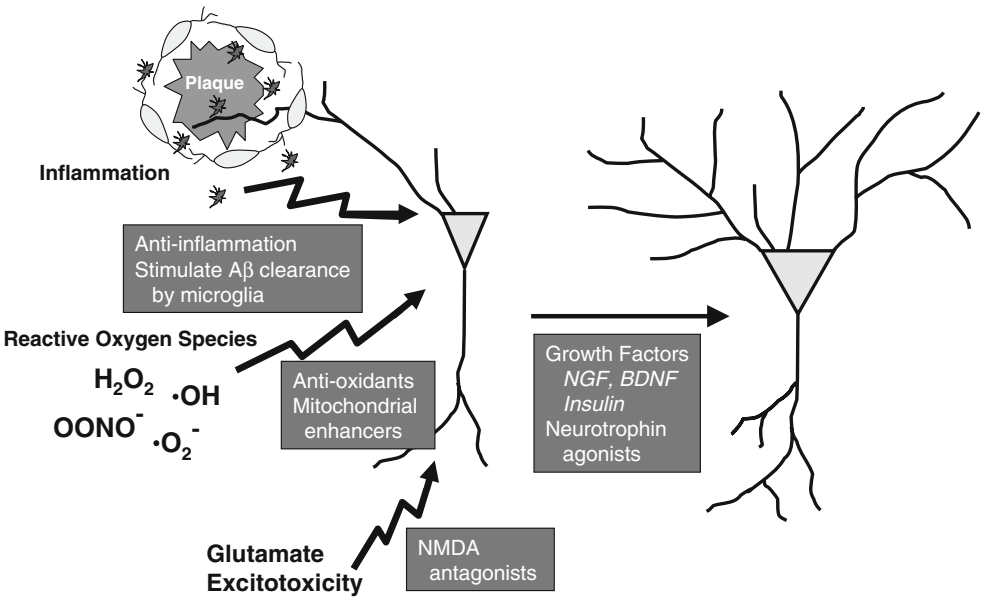

Fig. 3 Therapeutic approaches based on neurodegenerative changes in AD brain. Evidence exists for multiple toxic insults in AD, each of which is a potential target for therapy. In addition, methods to increase the number of synapses and dendritic spines are being investigated

low level, chronic inflammatory response via complement, cytokines, reactive oxygen species, eicosanoids, excitatory amino acids, proteases, nitric oxide, and acute phase proteins. These data led to clinical trials with traditional anti-inflammatory therapeutics, including prednisone, hydroxychloroquine, naproxen, celecoxib, and rofecoxib in AD, but all of the trials were negative [153]. Because inflammation in AD brain is relatively mild and involves different cell types than classical, peripheral inflammation, failure of these trials may not reflect the possible benefits of neuroinflammation inhibitors. New clinical trials may better address this hypothesis One example is the cytokine modulator, VP-025 (Vasogen Inc.), which is being prepared for phase II trials for AD [48]. PPARγ agonists (rosiglitazone, Ph III) may also have anti-inflammatory effects, in addition to normalizing insulin regulation and possibly also reducing Aβ levels [154]. Other potential anti-inflammatory agents include minocycline [155, 156] and LXR agonists [157]. The lipid-lowering statins may also have some anti-inflammatory effects, and initial clinical results with atorvastatin (Pfizer) have been promising [158]. A trial with lovastatin (Merck) is also underway [154]. Another approach involves stimulation of the neuronal cannabinoid receptor-1 (CB-1), which shows activity in preclinical models of neuroinflammation [159]. In contrast, some data suggests that stimulation of the inflammatory response may be beneficial in AD [160, 161]. Although most inflammation in AD is usually associated with Aβ due to the localization of activated astrocytes and microglia with plaques, inflammation may also play a role in tau-mediated aspects of the disease. A role for tau-mediated inflammation is suggested by recent work using an aggressive tauopathy model where inflammatory markers in microglia and neurons are increased prior to the development of tangles [162]. Interestingly, treatment of this model with FK506, an anti-inflammatory drug used to prevent transplant rejection, attenuated the inflammation, neuronal loss, and premature death associated in these mice. Preparations for clinical trials with FK506 are in progress.

Oxidative stress occurs in AD brain, leading to substantial oxidative damage to protein and lipid. Reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide, and hydroxyl radicals can be generated by activated glia, Aβ peptides (particularly when bound to copper and iron ions), excitotoxicity, and mitochondria [163]. Superoxide anions normally create significant oxidative stress in the brain since the brain normally consumes 20% of total oxygen, and 2% of oxygen is not reduced by mitochondria. Furthermore, mitochondrial function may be compromised in AD. For these reasons, agents that stimulate mitochondria or prevent oxidative damage are being developed [164]. The anti-diabetic rosiglitazone (Ph III) is one potential method to stimulate mitochondrial metabolism [151]. Potential antioxidants include mitoquinone (Antipodian Pharmaceuticals, Ph II) [48], vitamin E, and natural polyphenols, such as extracts from Ginkgo biloba, green tea, wine, blueberries, and curcumin (Ph II) [165]. Clinical trials with vitamin E, Ginkgo biloba extract, and omega-3 fatty acids have not shown strong beneficial effects in AD patients [166–168]. Since several antioxidant agents may be required for significant benefits for AD [165], clinical trials sponsored by the NIA are in progress using a combination of vitamin E, vitamin C, α-lipoic acid, and coenzyme Q (www.clinicaltrials.com).

Glutamate excitotoxicity is also hypothesized to play a role in AD. Glutamate is the primary excitatory neurotransmitter in the brain and overstimulation of glutamate receptors can cause seizures and neurodegeneration. Of the three types of ionotropic glutamate receptors, the calcium permeable NMDA receptors are most likely involved in AD. NMDA receptor blockade was first tested in clinical trials for stroke, but these therapies failed because NMDA receptor inhibition prevented normal glutamate signaling and caused sedation, hallucinations, and coma [169]. Based on these findings, a novel NMDA receptor antagonist, memantine, was developed. Memantine (Lundbeck/Forest) is a low affinity, selective, uncompetitive NMDA receptor antagonist with a fast off rate. Memantine only binds to the open channel at the magnesium inhibitory site. These properties allow memantine to block excessive stimulation at NMDA receptors without influencing normal receptor function [169]. In AD, a number of factors, such as inflammation, Aβ, and low ATP levels, are hypothesized to interfere with the usual magnesium block of NMDA receptors, leading to excessive activation without increases in glutamate levels [170]. Consistent with this hypothesis, AD patients have an increased incidence of seizures [171]. Memantine is an approved therapy for moderate to severe AD and is effective in patients with concomitant cholinesterase inhibitor use [172]. Neramexane (Merz/Forest), which has similar properties to memantine, is in phase III clinical trials [173]. Interestingly, preclinical studies show that Aβ oligomers induce oxidative stress via binding to NMDA receptors, an effect that is blocked by memantine [174]. In addition, seizures and abnormal neuronal excitability are observed in APP transgenic mouse models, along with compensatory inhibitory remodeling in the hippocampus [175]. The concept of dysfunctional neuronal networks in AD opens up many new therapeutic opportunities for AD [176].

Cognition Enhancers

In the 1970s and 1980s, it was discovered that acetylcholine (ACh) synthesis, ACh levels, and cholinergic receptors

were greatly reduced in AD brain [177]. These findings, combined with the known role of ACh in memory, led to the cholinergic hypothesis. The development and approval of four drugs for mild to moderate AD followed. They increase ACh levels by inhibiting acetylcholinesterase (AChE): tacrine (First Horizon Pharmaceuticals), donepezil (Pfizer), rivastigmine (Novartis), and galantamine (Janssen) [178]. Donepezil is now approved for later stages of AD as well. Although tacrine was the first drug approved for AD in 1993, it is rarely used due to hepatotoxicity [8]. In addition to AChE inhibition, rivastigmine inhibits butyrylcholinesterase, and galantamine allosterically modulates nicotinic receptors, although the importance of these additional activities to clinical activity is unknown [179]. While there have been a few clinical trials with direct comparisons between these three AChE inhibitors, there is no general consensus for differentiation between these therapies [8]. Although AChE inhibitors are widely used, only 25–50% of patients respond to therapy [2]. Current work in the field is directed at identifying therapeutics that combine AChE inhibition with other mechanisms [180]. One example is phenserine, a cholinesterase inhibitor that also reduces Aβ in preclinical models; phase III trial results with phenserine were not robust, and the status of further clinical development is unclear [181]. Huperizine A, derived from a Chinese herb, has neuroprotective activity in addition to AChE inhibition [182] and is currently in phase II trials [48]. Dimebon has several known activities in addition to AChE inhibition: histamine and NMDA antagonism and inhibition of mitochondrial permeability transition pores [183, 184]. Recent reports of phase II results for dimebon are promising, and phase III trials should begin soon [185].

In addition to cholinesterase inhibitors, efforts to increase cholinergic neurotransmission using muscarinic M1 agonists, M2 antagonists, and nicotinic agonists have been investigated (Fig. 4). Postsynaptic M1 receptors are spared in AD brain [177], while most M2 receptors are presynaptic autoreceptors that inhibit ACh release [186]. For these reasons, M1 agonists and M2 antagonists are sought for AD. In addition to effects on neurotransmission, M1 agonists may attenuate neuropathological endpoints [187, 188]. In particular, M1 agonists decrease Aβ in both experimental models and human CSF, possibly by stimulating α-secretase activity and inhibiting γ-secretase. M1 agonists also decrease tau phosphorylation in preclinical models, likely via activation of protein kinase C and subsequent inhibition of GSK3. Although M1 agonist development began at the same time as AChE inhibitors, no M1 agonists are approved for AD. The reason for the lack of successful M1 agonists for AD may be related to the lack of M1 selectivity and resultant intolerable side effects [189, 190]. Some phases I and II clinical trials for M1

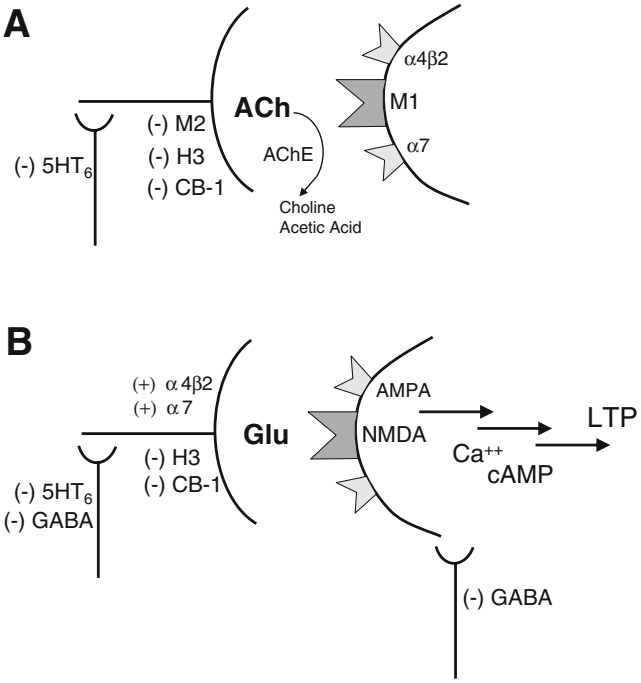

Fig. 4 Mechanisms of cognition enhancement for AD. **a** Mechanisms related to stimulation of cholinergic signaling, including AChE inhibitors, M1, α4β2, and α7 agonists, H3, CB-1, and $5HT_6$ antagonists or inverse agonists. **b** Mechanisms related to stimulation of glutamatergic signaling and formation of long-term potentiation (LTP), including Ampakines, α4β2, and α7 agonists, H3, CB-1, $5HT_6$, GABA antagonists or inverse agonists, PDE4 inhibitors, and calcium channel modulators

agonists continue, including NGX-267 (TorreyPines Therapeutics), P-58 (Phytopharm), and sabcomeline (Minster Research Ltd) [48]. M2 antagonists have been under development by Schering-Plough [191], but the status of those compounds, which cause tachycardia, is unclear [192].

Nicotinic agonists are also being developed as cognition enhancers based on the cholinergic hypothesis and epidemiologic data showing a reduced incidence of AD in smokers [193]. Unlike M1 receptors, though, nicotinic receptors are decreased in AD [177]. Since nicotine usage as a therapeutic is limited by side effects, including nausea/vomiting, cardiovascular effects, desensitization, and addiction, small molecule agonists of nicotinic receptors are being developed. Nicotinic receptors are ligand-gated ion channels that allow calcium flux, and their frequent presynaptic locations lead to enhanced release of glutamate, serotonin, gamma-aminobutyric acid (GABA), norepinephrine, dopamine, and norepinephrine. The α4β2 and α7 nicotinic receptors have both been implicated in learning and memory processes [194, 195]. Nicotinic agonists and partial agonists acting at both types of receptors improve performance in attention and working memory tasks in

preclinical models and humans [196, 197]. Clinical trials for both α4β2 and α7 agonists and partial agonists are in progress, although often with a primary initial indication for cognitive deficits associated with schizophrenia, where their effects on attention are likely to be of additional benefit [48, 194, 195].

Indirect means to enhance cholinergic and other neurotransmission are also being investigated for AD. Serotonin-6 (5-HT_6) receptor antagonists enhance signaling of ACh, glutamate, aspartate, dopamine, and GABA, probably via their effects on interneurons [198]. There are two 5-HT_6 antagonists in phase II clinical trials: SB-742457 (GlaxoSmithKline) and LY-483518 (Saegis Pharmaceuticals) [199]. Endocannabinoids are involved in retrograde signaling to the presynaptic terminal, where they inhibit release of glutamate, GABA, and ACh [200, 201]. AVE-1625, a CB-1 receptor antagonist, is also in phase II clinical trials [48]. In addition, histamine H3 receptor antagonists and inverse agonists are believed to increase ACh release by blocking presynaptic autoreceptors, and several agents are in early clinical trials [202].

Further approaches to cognition enhancement include various mechanisms to enhance LTP, a complex mechanism to increase the strength of synaptic connectivity, and likely related to memory formation [203]. Phosphodiesterase 4 (PDE4) inhibitors have been developed to increase cAMP levels in neurons. MEM-1414 (Memory Pharmaceuticals), a PDE4 inhibitor, is in phase II clinical trials [48, 204]. MEM-1003, also in phase II [48], is an L-type calcium channel modulator which may assist memory function by increasing the calcium mediated slow after hyperpolarization [205]. Ampakines® prolong synaptic responses and increase response amplitudes to AMPA, thereby enhancing LTP. Ampakines increase learning and memory in multiple preclinical models, and testing in humans has also shown significant memory enhancement in normal volunteers [206]. Phases I and II clinical trials for AD are in progress for Ampakines [48]. Inverse agonists at α5-containing $GABA_A$ receptors also stimulate LTP and enhance learning and memory in preclinical models [207]. $GABA_A$ inverse agonists and $GABA_B$ antagonists were initially investigated for possible use as cognitive enhancers when it was noticed that benzodiazepines are amnestic; SGS742, a $GABA_B$ antagonist is in phase II clinical trials [208].

Conclusions and Future Directions

There are numerous phases I and II clinical trials underway for a wide variety of new therapeutic approaches for the treatment of AD. Phase III clinical trials are in progress for γ-secretase inhibitors, an Aβ modulator, passive immunization of Aβ, and an Aβ aggregation inhibitor. These and other Aβ therapies should provide a robust test of the amyloid hypothesis in the next few years. Phase III trials with rosiglitazone will test a novel approach which may involve normalization of insulin signaling in the brain, anti-inflammation, and/or a reduction of mitochondrial stress. Cognition enhancers will remain an important part of AD treatment, even if disease-modifying therapies are successfully developed. Since it is unlikely that one drug will be able to cure AD, a combination of therapeutics will probably be optimal for the treatment of each patient.

In addition, it has become clear that a fraction of patients with mild cognitive impairment (MCI) are destined to transition to AD. These prodromal AD patients usually have a subtype of MCI designated as amnestic MCI. Research criteria using biomarker-enriching strategies allowing for identification of patients with prodromal AD have been proposed [209]. Because disease-modifying therapies will probably be more effective when used earlier in the disease process, it seems likely that an increasing number of therapeutics will be tested in prodromal AD patients. The rate of conversion from amnestic MCI to AD is 8–15% per year; however, the addition of CSF biomarkers can increase that rate to 27% per year [210]. The refinement of inclusion criteria using multiple biomarkers, such as CSF Aβ and Tau, magnetic resonance imagining, and positron emission tomography measurements of amyloid and hypometabolism, will be a focus and challenge of clinical research in the future [211]. These are exciting times for AD therapeutics, and the future is sure to bring many new and interesting targets, along with a few surprises.

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