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Novel targets for Alzheimer's disease treatment

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Summary

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which no cure exists. There is substantial need for new therapies that offer improved symptomatic benefit and disease-slowing capabilities. In recent decades there has been substantial progress in understanding the molecular and cellular changes associated with AD pathology. This has resulted in identification of a large number of new drug targets. These targets include but are not limited to therapies that aim to prevent production of or remove the beta amyloid (Aβ) protein that accumulates in neuritic plaques; prevent the hyperphosphorylation and aggregation into paired helical filaments of the microtubule-associated protein tau; and aim to keep neurons alive and functioning normally in the face of these pathologic challenges. We provide a review of these targets for drug development.

Keywords

Alzheimer's disease; dementia; treatment; beta amyloid; tau; therapeutics; beta secretase; gamma secretase; immunotherapy

Introduction

Recent research findings have led to greater understanding of disease neurobiology in Alzheimer's disease (AD) and identification of unique targets for drug development. Current therapeutic options aim at transmitter targets secondary to AD pathology. They offer limited efficacy and do not slow disease progression. The next generation of drugs for AD will alter the underlying disease course and/or provide greater symptomatic benefit. Targets for these drugs were identified in the study of AD pathophysiology and include but are not limited to the molecular events that result in the production and accumulation of the amyloid beta (Aβ) protein in neuritic plaques and the hyperphosphorylation, condensation and aggregation of the microtubule-associated protein tau in neurofibrillary tangles (NFTs). We review many of these targets, including those for which clinical development is ongoing or imminent. We begin by discussing current and emerging symptomatic targets,(**Table 1**) then we review targets with disease-modifying potential (**Table 2**).

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Targets Symptomatic Targets

Currently available therapies

Five medications are currently approved by the US Food and Drug Administration (FDA) for the treatment of AD. These agents, while providing important and useful symptomatic benefit, have limited or no impact on the underlying biology of AD, and no or limited impact on disease progression. Targets for these therapies are neurotransmitter-based. The acetylcholinesterase inhibitors (AChEIs) prevent the degradation of progressively decreasing acetylcholine (ACh) levels. AChEIs are effective throughout the course of AD.[1-8] The other class of approved medications includes only memantine, which regulates excitatory glutamatergic function and improves cognition in moderate-to-severe AD.[9,10] Administered together, these classes of medication may have enhanced symptomatic and long-term effects.[11,12] Altered neurotransmission in AD provides an array of targets for new drugs to improve cognition in the face of pathological challenge.

Nicotinic receptor agonism

The cholinergic system is well studied in AD. Neuronal nicotinic receptors (NNRs) for ACh are decreased in the AD brain[13,14] and this reduction correlates with cognitive impairment.[15] Most NNR agonists cross the blood-brain barrier.[16,17] NNR agonists improve cognition in small uncontrolled studies of normal volunteers[18] and AD patients.[19] Animal model studies suggest that these agents are as effective in improving cognitive performance as AChEI therapy.[20] Larger, more well-controlled clinical trials of NNR agonists will inform of their safety and efficacy in AD. No agents have been approved with NNRs as their target. A recent completed trial of one agent, AB-108, failed to meet its cognitive endpoints.

GABA receptor agonism and antagonism

As neurons that supply excitatory neurotransmission are lost in AD, inhibitory systems such as gamma aminobutyric acid (GABA) neurotransmission may go unchecked and result in cognitive impairment.[21] There is disagreement in the literature whether GABAergic neurons are less susceptible to the pathology of AD,[22-24] relative to excitatory neurons, or if levels of the neurotransmitter [25] and both $GABA_A$ and $GABA_B$ receptors[26] are decreased in AD. Regardless, agents that stabilize this system may modulate excitatory tone and reduce excitotoxicity. One selective $GABA_B$ receptor antagonist was clinically investigated in mild cognitive impairment,[27] but subsequently failed to demonstrate efficacy in AD.[28] Alternatively, inverse agonists of the $GABA_A$ receptor benzodiazepine-binding site (believed to reduce synaptic inhibition by reducing chloride ion flux) may enhance cognition.[29] Off target effects such as seizures and anxiety are a concern in compounds with inverse agonist or antagonist properties at the GABA receptor. A Phase II clinical trial of etazolate, a $GABA_A$ receptor modulator, recently completed enrollment. The synthetic GABA analog 3-amino-1-propanesulfonic acid (3APS; also known as tramiprosate or Alzhemed), was actively pursued as a treatment for AD, based more on its affinity for Aβ than any GABAergic properties.[30]

Serotonergic modulation

Of the 14 different serotonin (5-HT) receptor subtypes, several—including 5-HT_{1A}, 5-HT_4, and 5-HT_6—are expressed in areas important to learning and memory[31] and significantly decline in AD.[32-36] Levels of 5-HTRs may also change in very mild disease,[33,37,38] further implicating these receptors in the cognitive impairment associated with AD. 5-HTRs may also be altered in other dementias.[39] The role of the 5-HTRs is complex, including regulation of a variety of other neurotransmitter systems, such as ACh, dopamine, GABA, and glutamate.[31] In line with this complexity, both selective agonists [40,41] and antagonists [42-45] of 5-HTRs have beneficial cognitive effects in animal models. One selective 5-HT_{1A}R antagonist has reached Phase I investigation in man as a treatment for AD.[46] Results from a Phase II trial of a 5-HT_6 antagonist are encouraging.[47]

Histamine H3 receptor antagonism

Four subtypes of histamine receptor exist and among them the H3 receptor is highly expressed in human brain, including in areas important to memory function.[48] H3 functions as a presynaptic autoreceptor and a postsynaptic heteroreceptor and regulates histamine function as well as release of a variety of neurotransmitters. Antagonists and inverse agonists of the H3 receptor increase neurotransmitter levels of ACh, dopamine, norepinephrine, and 5-HT.[49] Expression of H3 receptors in the periphery is limited, relative to expression in the brain. Unlike many other receptor systems, H3 receptor levels are maintained through the course of AD progression.[50] Development of H3 antagonists is therefore a promising target for AD therapies as well as a variety of other CNS disorders.[51] Clinical trials of H3 antagonists in AD are now underway.[49](www.clinicaltrials.gov)

Phosphodiesterase inhibition

Improving synaptic function may provide a target for symptomatic therapy in AD. The cyclic-AMP response element–binding protein (CREB) is a transcription factor that is important to memory[52,53] and down-regulated in models of altered synaptic function related to AD.[54] In transgenic animal models of AD, synaptic long-term potentiation (LTP) can be restored through enhancement of the CREB pathway by increasing cGMP through inhibition of phosphodiesterase (PDE). This appears to be true for pan-PDE inhibitors such as caffeine,[55] and for more specific PDE inhibitors.[56,57] New inhibitors of specific PDE subtypes have been identified,[58] but previously approved agents such as those indicated for treatment of erectile dysfunction are also being investigated.[57,59] The wide use of the latter suggests the likely safety of this class of agents in elderly subjects.

Metabolic enhancement

Brain hypometabolism is an early consequence of AD pathology.[60,61] The early occurrence of cerebral hypometabolism in AD makes it unlikely to result from neuronal loss but instead a result of synaptic dysfunction. Therefore, increasing glucose metabolism in the AD brain may provide symptomatic improvement. Glucose administration improves memory performance in healthy elderly participants.[62] In AD patients, however, glucose administration failed to improve cognitive performance.[63] Provision of alternative energy supplies such as ketogenic substances may improve brain metabolism and cognition.[64]

One ketogenic dietary agent has recently been shown in a double-blind placebo-controlled trial to improve symptoms in AD,[65] and has subsequently received marketing permission from the U.S. Food and Drug Administration as a medical food.

Treatment with insulin also improves memory performance in AD.[63] The dysregulation of insulin in diabetes appears to increase risk for AD[66] and the insulin-degrading enzyme (IDE; also known as insulysin) also degrades Aβ.[67,68] These facts led to the investigation of the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist rosiglitazone as a treatment for AD.[69] Larger trials of rosiglitazone were made more difficult by cardiovascular health risks for this class of agents and one trial recently failed to demonstrate efficacy.[70] Direct intranasal administration of insulin also can improve cognitive function in AD.[71] Larger studies will be needed to confirm the symptomatic efficacy of intranasal insulin administration.

Disease Modifying Targets

Beta Amyloid

With extensive basic and clinical science support, the amyloid hypothesis remains the most prominent theory of AD pathology and target for drug development.[72-76] Central to this hypothesis is the proteolytic processing of the amyloid precursor protein (APP).[77] Posttranslational modification of APP occurs through two paths, beginning with cleavage by either α- or β-site enzymes. In either case, the produced C-terminal fragment is membrane-tethered and further processed within the transmembrane region by gamma secretase. Gamma secretase cleavage of the α-secretase product yields an apparently non-toxic protein fragment (p3), whereas the product of sequential beta-site cleavage enzyme (BACE) and gamma secretase cleavages is the 38-43 amino acid fibrillogenic amyloid beta protein (Aβ).[77] The 42-amino acid $A\beta_{42}$ is most prone to aggregation, found in the core of neuritic plaques, and—when aggregated into oligomers—is largely considered the key pathological component in AD. Deposits of Aβ can occur anywhere that APP, BACE, and gamma secretase are found, and this includes both intraand extracellular spaces.[78] Aggregates of Aβ are toxic to synapses and neurons. Initial stages of aggregation, ranging from dimeric to dodecomeric soluble aggregates, are believed to be most toxic and are collectively referred to as Aβ oligomers.[79]

The amyloid hypothesis is supported by the largely identical clinical and pathologic phenotype among the sporadic late onset AD and the rare inherited early onset form of AD that results from autosomal dominant mutations to the genes for APP and two of the subunits in gamma secretase (presinilin 1 and 2).[73,80-82] Over 150 mutations that result in this familial AD (fAD) have now been identified, all of which exclusively involve these three genes integrally involved in Aβ production.[81] The largest number of disease-modifying drug candidates for AD target APP processing and Aβ: limiting production of the toxic form of Aβ; removing Aβ from the brain, through degradation, transport, or immunotherapeutic mobilization; or preventing the toxic effects of Aβ.

Aβ Production

Alpha Secretase activation—Increasing production of non-amyloidogenic products of APP processing through activation of α-secretase could provide a drug target for reducing pathologic Aβ. Few compounds have been identified that successfully activate α-secretase. Among those that have, receptor agonists for subtypes of muscarinic ACh receptors (mAChR) are appealing. It is clear that among the five different mAChR subtypes, M_1 is highly expressed in hippocampus and cortex and involved in cognition.[83] Loss of M_1 function induces cognitive impairment, and agonism of the M_1 receptor is a logical target for cognitive enhancement.[84] M_1 (and M_3) receptor agonism also regulates APP processing by increasing α-secretase activity and inhibiting α-secretase.[85,86] It is not yet known if mAChR function in AD is impaired and will limit the efficacy of selective agents that target M_1.[87] Treatment of AD patients with an M_1 agonist, however, reduces CSF Aβ[88] and M_1 agonists are in development for AD.[87]

Beta Secretase inhibition—Cleavage of APP by BACE (also known as α-secretase and memapsin-2) is the first step in the proteolytic processing of APP, making it the ideal position in the cascade to intervene and halt production of all posttranslational products. BACE activity is increased in sporadic forms of AD.[89-91] BACE knockouts have limited phenotypic changes beyond reduced levels of Aβ,[92,93] suggesting that potent inhibitors may have limited side-effect profiles. Development of agents capable of inhibiting the multisite activity of BACE on its APP substrate has been difficult. Successful inhibition initially required large molecules (>500KDa) that were unable to cross the blood-brain barrier.[94] Highly lipophilic, smaller orally available agents that have access to the CNS have recently been developed, however, and such agents are currently in human clinical trials.[95]

Gamma Secretase inhibition—The rationale for targeting gamma secretase is similar to that of BACE; prevention of gamma secretase action inhibits posttranslational processing of APP and formation of Aβ. Gamma secretase is a four-part complex, consisting of the membrane proteins presenilin-1 or -2, nicastrin, Aph-1, and Pen-2.(Reviewed in [96]) Of these, presenilin serves as the catalytic subunit. Presenilin-mediated catabolism is critical not only to APP proteolysis but also to a variety of other transmembrane proteins including the Notch signaling receptor. Cleavage of the Notch transmembrane receptor by presenilin permits nuclear translocation of the Notch signaling protein. Presenilin knockouts are lethal and phenotypically similar to Notch knockouts, suggesting the critical role of presenilin cleavage in Notch signaling.[97] The role of Notch in development is well described and includes regulating proliferation, cell fate decisions, and cellular growth.[98-100] In adult physiology Notch signaling continues to play a major role, and potent inhibition of Notch cleavage and signaling by presenilin/gamma secretase inhibitors may result in intolerable or dangerous adverse events related to gastrointestinal, lymphatic, skin, and immune system toxicity.[101] Therefore, targeting gamma secretase is a binary challenge. Activity must sufficiently lower Aβ to have clinical impact (the degree of Aβ-lowering to accomplish this is not yet known). Moreover, this activity must be selective to brain gamma secretase and not result in intolerability or dangerous side effects due to Notch toxicity. To this point, the primary strategy to balance efficacy and tolerability has been to pursue agents with minimal

Notch activity. Multiple agents have now entered clinical trials. [102-104] Gamma secretase inhibitors are capable of reducing plasma Aβ[105] and lowering CSF production of Aβ[106,107] in AD patients and normal volunteers, respectively. LY450139 is a gamma secretase inhibitor currently in Phase III clinical trials.(www.clinicaltrials.gov)

Alternatively, agents that modulate gamma secretase (without directly preventing cleavage) may selectively lower Aβ without altering Notch activity. Early studies identified a variety of nonsteroidal anti-inflammatory drugs (NSAIDS) and NSAID-like compounds that could reduce Aβ production *in vitro*, that did not act on Notch or on the cyclooxygenases. [108,109] Among these, R-flurbiprofen advanced through clinical development but failed to demonstrate efficacy in a large phase III clinical trial.[110,111] Brain penetration of the agent may have been inadequate. Although these results were disappointing, gamma secretase modulators may still hold promise as a therapeutic class. Target sites other than presenilin may be plausible and drugs that act through conformational inhibition, rather than direct catalytic inhibition, would not induce Notch-related toxicity.[112] Additionally, Kukar and colleagues recently demonstrated that some NSAIDs can modulate gamma secretase activity through APP binding, suggesting another potential path to reduce Aβ without Notch toxicity.[113] Drugs that block gamma secretase activity through substrate binding may have the added benefit of acting as Aβ aggregation inhibitors.

Degradation of Aβ

Once present in the brain, the toxic form of Aβ must either be degraded or removed to prevent the clinical development of dementia.[114] Multiple endogenous pathways for Aβ degradation exist and include neutral endopeptidase (also known as neprilysin)[115,116], IDE, endothelin-converting enzyme,[117,118] angiotensin-converting enzyme (ACE), and metalloproteinase 9. Of these, neprilysin and IDE are thought to be the primary regulators of Aβ degradation, as well as the optimal drug targets.[119] Levels of Aβ degrading enzymes are reduced in AD.[120] Further, transgenic animals that lack the proteases key to Aβ degradation show increased brain Aβ deposition in a gene dose-dependent fashion[121], whereas APP transgenic mice that overexpress the neprilysin transgene demonstrate increased Aβ degradation (seen as a reduction in total soluble Aβ and plaque burden).[122] These animals, however, showed no reduction of oligomeric Aβ and no improvement in memory performance relative to APP mice.[122] APP transgenic mice engineered to overexpress IDE and neprilysin have reduced Aβ levels, virtually no plaque formation, and reduced astrogliosis, microgliosis, and dystrophic neurites.[123] These transgenic animals also show improved spatial memory in at least some models.[124]

Increased levels of neprilysin through viral vector delivered gene expression can lower Aβ in mouse models of AD.[125,126] Alternatively, molecular regulators of neprilysin levels *in vivo* could provide a more easily accomplished pharmacologic target.[127] Cabrol and colleagues recently completed a high-throughput screen in which they identified multiple small molecule activators of IDE,[128] suggesting that pharmacological manipulation of Aβ degradation enzymes is a realistic target for disease modification in AD. Given the number of degrading enzymes, it is important to demonstrate that inhibiting one pathway is adequate for a therapeutic benefit. Alternatively, multiple degradative pathways could be targeted.

Removal of Aβ

Vaccination—Vaccination with the full length Aβ peptide decreases amyloid burden and abrogates learning and memory impairment in animal models of AD.[129,130] Recent animal model investigations suggest that vaccination can reduce amlyoid burden as well as neurofibrillary tangle pathology.[131] A clinical trial of Aβ vaccination (AN1792) in 300 mild AD patients was halted due to a 6% incidence of T-cell mediated meningoencephalitis.[132] Preliminary results suggested a clinical benefit in participants who received therapy and generated antibodies against Aβ.[133] Analysis of the primary outcomes at the time of trial interruption demonstrated no drug-placebo difference.[134] Long-term follow up of survivors suggested a benefit in activities of daily living, quantified with the Disability Assessment for Dementia scale, among antibody responders.[135] Long-term follow-up to autopsy of the first subjects to die, however, demonstrated that there was no impact on clinical progression to advanced dementia, despite removal of plaque burden in the cortex among antibody responders.[136,137] Further, initial pathological analysis suggested that while Aβ removal was successful, NFT pathology was unaltered.[138] These findings have sparked continued debate as to whether Aβ provides the appropriate target for AD therapies.[139] Nevertheless, clinical development of immunotherapies for AD, including active vaccinations, remains a major research focus. Full length Aβ vaccinations, as well as peptide fragment vaccinations, are in development.[28]

Passive immunization—Passive immunization attempts to provide the Aβ-lowering and potential clinical benefit of vaccination, while avoiding the T-cell mediated response. Transgenic mouse studies confirm that the beneficial effects of vaccination including removal of Aβ burden, reductions in aggregated tau, and amelioration of cognitive deficit can be achieved with passive antibody therapy.[140-142] The exact mechanism of action for antibody therapy remains elusive, though several not mutually exclusive hypotheses have basic science support. Activation of microglia enhances breakdown of Aβ. The occurrence of “moth-eaten” plaques and increased immunohistochemical evidence of microglial response in vaccinated antibody responders that have come to autopsy from the AN1792 study support the hypothesis that immunotherapy enhances microglial response against Aβ.[136] Similarly, microglial activation occurs in response to vaccination [143] and passive immunization[144] in transgenic models of AD and is critical to reducing Aβ burden.[145] Additionally, antibodies may trap Aβ in the brain blood vasculature and transport it to the periphery where it can be more effectively degraded. Deglycosylated antibodies, which fail to activate the microglial response, persist in their ability to remove Aβ from the brains of mouse models of AD.[146,147] Similarly, passive immunization of transgenic animals that lack the Fc receptor necessary for microglial activation exhibit Aβ removal.[148] A variety of antibody therapies are now in clinical development, with two monoclonal antibody therapies in Phase III trials—bapineuzumab and solanezumab.

Interestingly, plaques in the brains of untreated AD patients are decorated with IgG antibodies, and these antibodies appear to elicit a microglial response.[149] Although this is insufficient for staving off clinical impairment, an inverse relationship exists between IgG level and plaque burden.[149] Therapeutic use of naturally produced autoantibodies in the form of intravenous immunoglobulin (IVIg) as treatment for AD is a current area of clinical

investigation. IVIg treatment increased plasma and decreased CSF levels of Aβ in a study of 8 AD patients.[150] IVIg is in a large multisite clinical trial in the US.

Aβ Transport

Beside age, the most well established risk factor for AD is the apolipoprotein E (ApoE) genetic status. Three isotypes of ApoE exists: ε2, ε3, and ε4. ε2 and ε4 are distinguished from ε3 by only single amino acid substitutions.[151] Persons carrying one or two copies of the ε4 allele are at increased risk to develop AD and to do so at an earlier age.[152] In those with AD[153] and those at risk for AD,[154] ε4 carrier status results in increased Aβ deposition in the brain. Apolipoproteins play a role in Aβ metabolism and transport.[155] Apolipoproteins do not cross the blood brain barrier (BBB),[151] but may regulate passage of Aβ between the CNS and the periphery. The extent to which the different isoforms of ApoE bind Aβ is debated.(reviewed in[155]) ApoE ε4 may increase passage of Aβ from blood to brain.[156] Mouse models that overproduce and deposit Aβ, when combined with transgenic animals that lack ApoE, have reduced Aβ deposition.[157] Synthesized compounds that prevent ApoE binding to Aβ reduce plaque deposition and memory impairment in animal models of AD.[158] This may provide an avenue for therapeutic intervention in AD; though benefit may depend on ε4 carrier status.

It is likely that ApoE carries Aβ to a receptor that facilitates passage across the BBB.[114] The low-density lipoprotein receptor-related protein (LRP) seems to be involved in such receptor-mediated passage of Aβ.[159] Antibodies against the LRP reduce Aβ efflux from the brain.[160] With age LRP expression is decreased and LRP-mediated Aβ efflux is reduced, increasing risk for Aβ build up and clinical onset of AD.[160] Mechanistically, LRP has been shown to bind, endocytose, and trancytose Aβ, though questions remain over LRP affinity for $A\beta_{40}$ versus $A\beta_{42}$.[161] Nevertheless, peripheral administration of soluble LRP in AD as a mechanism to pull Aβ out of the brain has been proposed as a potential therapy.[162]

Alternative to enhancing Aβ removal from the brain, it may be useful to prevent its entry to the CNS from peripheral sources. The receptor for advanced glycation end-products (RAGE) is a multiligand receptor expressed by a variety of cell types throughout the body[163] and brain.[164,165] RAGE binds Aβ with high affinity and expression of the receptor is increased in AD.[164,166] Preventing ligands from binding RAGE lowers brain levels of Aβ.[167] Therefore, a variety of compounds that aim to inhibit RAGE interaction with its endogenous ligands or provide soluble alternative receptor binding are in development as treatments for AD. One such compound is currently being investigated in a Phase II clinical trial.

Thus, brain levels of Aβ are determined by a complex equation including production, removal, and degradation. While production of Aβ is largely understood, removal and degradation are multifactorial the role of each possible pathway remains to be fully comprehended. The balance (or imbalance) between the mechanisms by which brain Aβ levels are maintained, and the causal link between this balance and AD remains uncertain and debated.[168]

Aβ Oligomerization

The most synaptotoxic form of Aβ is neither the constitutive monomeric form, nor the fibrillar form deposited in plaques.[79,169-171] The greatest Aβ-derived toxicity results from initial aggregation stages when monomeric Aβ first oligomerizes into dimers, trimers, and other high-molecular-weight combinations. Oligomer reduction is the most compelling target in the Aβ cascade; reducing fibrillar Aβ may have little or no cognitive benefit. Animals with reduced plaque burden but high oligomer levels have no improvement in cognitive function.[170,172] It is plausible that Aβ plaques act as an endogenous sink, removing toxic oligomeric Aβ from the parenchyma[170] or they may serve as reservoirs for oligomeric Aβ. Estimates of how much total Aβ is soluble at any one time are as low as 5%. In animal models, reduction of soluble Aβ levels by 25% reduced plaque formation but had no effect on plaque burden.[173]

The aggregation properties of Aβ are fairly well established[174-176] and provide anti-aggregation targets for drug development.[177](**FIGURE**) Glabe and colleagues recently identified unique inhibitors capable of preventing oligomerization, fibrillization, or both.[178] Further, single agents may be able to decrease oligomerization while promoting fibrillization.[179] These findings support the hypothesis that multiple pathways of Aβ aggregation exist and may need to be further explored to optimize drug development that aims to reduce oligomers.

The only agent aiming to prevent Aβ aggregation thus far tested in a large Phase III trial—tramiprosate—failed to meet its primary endpoint. It remains unclear if this agent lacked efficacy because it prevented fibrillization but not oligomerization of Aβ, or if Aβ is an inappropriate target.[28] Additionally, trial irregularities—including abnormal variance among study sites and lower than expected placebo decline—make it difficult to draw conclusions about drug efficacy.

A variety of other agents that aim specifically to prevent the oligomerization of Aβ are also in development. Cyclohexanehexol (also known as AZD-103) prevents oligomerization *in vitro*,[180] abrogates Aβ oligomer–induced impairments to LTP,[181] and alleviated AD cognitive impairment in a mouse model.[181,182] AZD-103 was safely tolerated in a human Phase I trial.

Other compounds may similarly inhibit oligomerization of Aβ, including grape-derived polyphenols,[183,184] omega-3 fatty acids such as docesahaexonic acid (DHA),[185] and curcumin.[185] In addition to potentially being aggregation inhibitors, each of these compounds are potent antioxidants and anti-inflammatory agents.[186,187] Epidemiologic studies of dietary intake[188-191] and comparisons of geographic regions where consumption is high for these compounds[192,193] suggest that consistent consumption can reduce risk for AD. Supplementing the diets of transgenic animals with these compounds confirms that they can reduce AD pathological burden in the brain.[194-196] For these reasons each of these classes of compounds have been or will be tested in human clinical trials as therapies for AD.[80](www.clinicaltrials.gov)

Bush and colleagues[197] have proposed a metal-related hypothesis of Aβ aggregation. In this model, metal ions such as copper and zinc, released with synaptic activity, promote the oligomerization of monomeric Aβ.[198,199] Such metal ions are elevated in AD[200] and are localized to plaques.[201] Based on these findings, a metal protein attenuating compound (MPAC) was tested in a clinical trial.[197] PBT2 demonstrated initial efficacy in AD, lowering CSF levels of Aβ and mitigating cognitive deterioration relative to placebo.[202-204] The specific mechanism of action of PBT2 remains debated,[205] however, and roles for the drug beyond local metal chelation have been proposed. At least one report suggests that clioquinol (another MPAC) may act in the mitochondria to inhibit enzymatic activity believed to underlie cellular aging.[206]

Tau and Neurofibrillary Tangles

The second pathological hallmark of AD is the intracellular neurofibrillary tangle (NFT). NFTs are condensed cytoskeletal inclusions composed of hyperphosphorylated paired helical filaments of the microtubule-associated protein tau (MAPtau or tau). In contrast to the axon-specific expression of tau in developing and healthy neurons,[207], in AD hyperphosphorylated tau is translocated to the somatodendritic compartment. Phosphorylation of tau is critical to its function, but hyperphosphorylated tau no longer binds to microtubules, instead aggregating into paired helical filaments.[208] The result is a general instability of microtubules and disruption of axonal transport that leads to neuronal injury and cell death. Increased levels of phosphorylated or total tau in the CSF are strong indicators of neurodegenerative disease or injury.[209] Though it is argued that a stronger link exists between NFT topography and clinical phenotype,[210] development of therapies targeting NFTs has lagged behind those that target Aβ.[211] Therapies targeting tau aim to reduce, stabilize, or prevent hyperphosphorylation or aggregation of the protein.

Total Tau

Multiple basic science models suggest that reducing tau can alleviate Aβ-dependent or Aβ-independent cognitive impairment in neurodegenerative models.[212,213] Given that tau is a constitutive part of the cell, however, removing tau entirely is not likely to be a realistic target.

Tau Aggregation

Oligomers of tau are part of normal functioning for the microtubule-associated protein and departure from this oligomeric structure into more aggregated compounds may represent the pathological step in tau processing.[214] Classes of agents that may act to prevent tau aggregation include anthraquinones, polyphenols, aminothienopyridazine, and phenothiazines.[215] Wischik and colleagues have begun clinical development of the phenothiazine methylene blue as a treatment for AD.[216,217] The initial clinical trial of this agent failed to meet its prespecified endpoints but long-term observations and biomarker studies suggested possible benefit. Clinical development in AD continues. Methylene blue also decreases Aβ oligomers *in vitro* by increasing fibrillar but not monomeric Aβ.[179]

Tau Hyperphosphorylation

Most of the drug development aiming at tau has targeted reducing hyperphosphorylation. Phosphorylation of tau can occur at many unique sites of the protein and through multiple pathways.[218-220] Among the various kinases involved in hyperphosphorylation of tau, glycogen synthase kinase 3 beta (GSK-3β) and the cyclin-dependent kinase-5 (cdk5) both target multiple phosphorylation sites on tau,[221] suggesting therapeutic potential for preventing the formation of NFTs.[219] Interactions between GSK-3β and cdk5 exist, and will require further evaluation to optimize treatments aimed at these kinases.[222,223]

Lithium and valproate are commonly used agents that have inhibitory action on GSK-3β and may stabilize tau.[211] Small and open label studies have suggested efficacy of these agents as therapies for cognitive and behavioral symptoms in AD.[224-226] Larger more controlled studies have failed to confirm efficacy for both lithium[227] and valproate.[228]

Agents with more appealing tolerability and safety profiles but still able to inhibit GSK-3β and stabilize tau are likely to reach clinical investigation in the near future. Recent findings suggest that caffeine inhibits GSK-3β,[229] in addition to inhibiting PDE (see above). Given epidemiologic findings of decreased incidence of AD in heavy caffeine users[230] and efficacy of caffeine in Aβ transgenic animal models,[231,232] further exploration of caffeine as a therapy for AD is warranted.

Phosphatases dephosphorylate tau and may offer an alternative to inhibition of hyperphosphorylation. Protein phosphatase 2A (PP2A) has been described to play a large role in regulation of tau phosphorylation and is decreased in AD.[233-235] Inhibition of PP2A is sufficient to result in hyperphosphorylation of tau, formation of NFT-like structures, and memory impairment in animal models.[236,237] Multiple PP2As exist and agents that can increase activity of these phosphatases, perhaps by targeting the endogenous proteins that inhibit their activity, are logical drug candidates for AD treatment.[238,239]

NAP is an 8 amino acid peptide (with N-A-P representing the first three amino acids in the peptide) believed to represent the active component of the glial-derived activity dependent neuroprotective protein (ADNP).[240] Unlike other trophic factors, which work via receptor-based mechanisms of action, NAP enters the neuron and interacts directly with microtubules.[241] NAP has potent ability *in vitro* to rescue neurons from Aβ-induced cell death[242] and also can reduce tau phosphorylation.[243] NAP treatment has demonstrated efficacy in the triple transgenic mouse model of AD.[244,245] Intranasally administered NAP treatment can cross the BBB[246] and has reached clinical investigation.[240]

It remains unclear whether therapies that alleviate Aβ pathology only or tau pathology only will ameliorate (or prevent) the cognitive decline in AD.[212,247] It is also important to note that therapies that successfully target tau may have applications beyond AD. Tau hyperphosphorylation is common in other forms of dementia, creating the possibility that successful tau-stabilizing agents will offer therapeutic efficacy in a variety of neurodegenerative conditions, including the frontotemporal dementias, progressive supranuclear palsy, and corticobasal degeneration.[248,249]

Neuroprotection

Neuroprotective strategies aim to ensure cell health in the presence of disease-specific pathology. These include therapies that reduce inflammation or other downstream markers of AD pathobiology. For example, epidemiologic findings have suggested disease-preventing properties for the non-steroidal anti-inflammatory drugs (NSAIDs)[250,251] and the statins.[252,253] The mechanisms by which these agents reduce AD, if they do, are not entirely clear. The anti-inflammatory properties of NSAIDs and the cholesterol-lowering properties of statins both might be useful in preventing or treating AD. Both classes of agents, however, may also reduce Aβ.[254] Prospective randomized placebo-controlled studies of NSAIDs have thus far failed to demonstrate efficacy as treatments,[255-257] although some studies were halted for safety concerns and thus prevented full examination.[258] There is a more mixed literature relating to statins. The Religious Orders Study [259] and Cardiovascular Health Study[260] found no effect of statin use on AD occurrence or neuropathology, but Li and colleagues demonstrated a reduced risk for NFT burden in statin users when examining participants followed longitudinally.[261] A prospective trial of 67 mild-to-moderate AD patients randomized to atorvostatin or placebo suggested a clinical benefit with treatment.[262] As a result of these findings, a larger prospective trial of atorvastatin and donepezil was initiated but failed to show a drug-placebo difference.[263,264]

Mitochondrial dysfunction plays a clear role in cell death.[265,266] Cellular aging and neurodegenerative disease mutate mitochondrial DNA, alter mitochondrial membrane permeability, and generally impair mitochondrial function.[267,268] In AD, soluble Aβ enters the mitochondria,[269] and results in mitochondrial membrane dysfunction, Ca^{2+} entry, reduced energy production, and oxidative stress that may ultimately lead to neuronal cell death.[268,270] Agents that stabilize the mitochondrial membrane, prevent mitochondrial DNA mutation, remove reactive oxygen species, or improve mitochondrial function may prevent age-related cellular changes and counteract neurodegenerative disease, including AD. Dimebon (dimebolin, latrepirdine) is a non-selective antihistamine previously approved in Russia now being developed for AD and Huntington's disease that may target mitochondrial membranes.[271] In addition to low affinity effects on AChE and glutamate receptors, dimebon appears to stabilize mitochondrial permeability transition pores, preventing ionic influx.[267] Doody and colleagues recently published results from a clinical trial of this agent in 183 mild-to-moderate AD patients.[271] After 26 weeks patients receiving therapy showed improvement relative to placebo on the mini mental status examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCSADL), Clinician Interview-Based Impression of Change (CIBIC)-plus, and Neuropsychiatric Inventory (NPI) outcomes. Blinded extension study to 12 months[271] and open label extension to 18-months[272] demonstrated continued benefit of therapy. Phase III testing of this agent is on-going.

Histones are proteins that organize chromatin within the cell nucleus. Histone regulation occurs by a variety of epigenetic modifiers, including methylation, acetylation, phosphorylation, ubiquitination, and ribosylation.[273] Among these, the balance between

histone acetyltransferase (HAT) and histone deacetylase (HDAC) activity may be particularly relevant to synaptic function and memory, and may become unbalanced in AD and other neurodegenerative diseases.[274] Moreover, reestablishing this balance or increasing histone tail acetylation through inhibition of HDACs may facilitate memory recovery through synapse formation and dendritic growth.[275] Multiple classes of HDACs exist, composed of at least 10 subtypes. Recent work suggests that the HDAC2, but not HDAC1, subfamily of deacetylases is critical to synaptic function and may be an appropriate target for development of new therapies.[276] One small trial of nicotinamide, a class III HDAC inhibitor, improved memory in a triple transgenic mouse model of AD.[277] A trial of this agent has been initiated in AD patients.(www.clinicaltrials.gov)

Neurotrophic factors have long been known to promote survival and growth of neurons during CNS development, leading to great interest in the therapeutic application of these factors in the diseased adult brain.[278] Despite *in vitro* and animal model successes, trophic factor therapies have thus far failed in clinical investigation, either as a result of lack of efficacy or intolerability, in amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and other neurodegenerative disorders. [278-280] Issues with growth factor tolerability likely result from potent but often nonspecific neuritogenic activity.[281,282] Recent development of more targeted delivery approaches will allow for further evaluation of neurotrophic factor efficacy. In AD, nerve growth factor (NGF) delivery to the trk-A receptor-expressing cholinergic neurons of nucleus basalis of Meynert (NBM), which are known to be susceptible early in disease,[283] may increase cell survival and enhance cholinergic supply to the neocortex and hippocampus.[284-286] An initial trial of intracerebroventricular infusion of NGF offered limited efficacy and notable side effects. [281] Implantation of autologous fibroblasts genetically engineered to express NGF reduced the rate of cognitive decline and increased regional cerebral metabolism.[284] Focal delivery of gene therapy using adeno-associated virus (AAV)-delivered neurotrophic factor DNA provides long-term expression of the transgene and protein production, with minimal trophic factor diffusion.[287-289] Clinical investigation of NGF gene therapy as a treatment for AD is on-going. Similarly, Cerebrolysin, a compound that mimics neurotrophic factor effects has been tested in a clinical trial and results suggest improved cognition in AD.[290]

Five- Year View

To understand the immediate future in AD drug development, assessment of the current status of the field is necessary. We are on the cusp of a tremendous health care crisis as a result of AD. Already the source of immense societal cost, the number of AD cases in the US and worldwide is expected to triple in the coming decades. We are also on the brink of drastic improvements in our armamentarium to treat and, perhaps, prevent AD. The field currently pursues new treatments as well as improvements in diagnosis. Simultaneous advances in these two arenas will allow us to at least delay the onset of this debilitating disorder through preclinical identification and initiation of disease-slowing treatments. Successful development of an agent capable of delaying AD onset by 5 years will reduce the total number of cases by half and an agent that can delay onset for 10 years will essentially eradicate AD.[291]

Given the urgent need for and strong focus on developing new classes of therapy for AD, there is opportunity for rapid translation of basic science findings into clinical investigation. Clinical trials in AD have met great challenges. A number of agents through to hold promise have reached large-scale trials of efficacy only to fail to meet primary outcomes. Some of these have been positive studies (able to demonstrate definitive outcome) of negative results. Other cases, however, are less clear whether the drug failed or the trial did. Questions have arisen about optimal design for trials of disease modifying therapies, placebo decline, statistical power, and study conduct. Moreover, every failed trial in AD causes researchers to ask “are we intervening early enough?” Many of these issues remain unresolved.

The next five years will almost certainly bring new findings that will enhance our target selection in AD. A large number of agents are now in the final phase of clinical development (**Table 3**) and in the next 5 years it is likely that we will be able to confirm efficacy for one or more agents capable of at least mildly slowing disease progression. When this occurs, clinical trials investigating how best to use these agents and when and in what order to initiate their use will be critical. Only after such therapies have completed clinical investigation, however, will we have new treatments to offer our patients. Thus, it is critical that all physicians who care for AD patients refer eligible patients for participation in clinical trials.

Finally, debate remains over the definitive cause of the cognitive impairment in AD. It is conceivable that only through large-scale studies of agents for which cellular and molecular mechanisms of action can be confirmed will such debates finally be put to rest. That is, if a drug efficiently and completely removes amyloid from the AD brain and this entirely halts disease progression, ameliorates cognitive decline, or reverses disease effects, it will suggest that amyloid, in and of itself, is the primary culprit in disease pathology leading to clinical phenomenology. While this example is an unlikely scenario, it is clear that we will also make great strides in better understanding the pathology of AD with the development of agents that successfully prevent Aβ production or oligomerization, remove Aβ from the brain entirely, prevent tau hyperphosphorylation or tau aggregation (and a great many other potential mechanisms).

Expert Commentary

AD is a relentlessly progressive neurodegenerative disease that is increasing in prevalence rapidly. Elucidation of the pathophysiology of AD has resulted in better understanding of the preclinical events that lead to ostensible dementia. This pathophysiology includes the molecular and cellular events that lead to and result from the formation of amyloid plaques and neurofibrillary tangles. A multitude of drug targets relate to AD biology have been identified, including those for which cognitive symptom improvement is the goal, and others for which disease slowing is the goal. Only through clinical testing of such agents will these targets be validated and true causal pathology of disease be confirmed.

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KEY ISSUES – bulleted executive summary

- No effective disease-modifying therapy for AD exists
- A multitude of targets for new AD therapies have been identified in recent years
- Testing of new agents in clinical trials is the rate-limiting step to new therapies
- Clinical examination of new agents may resolve some of the disputes over causal pathology in AD

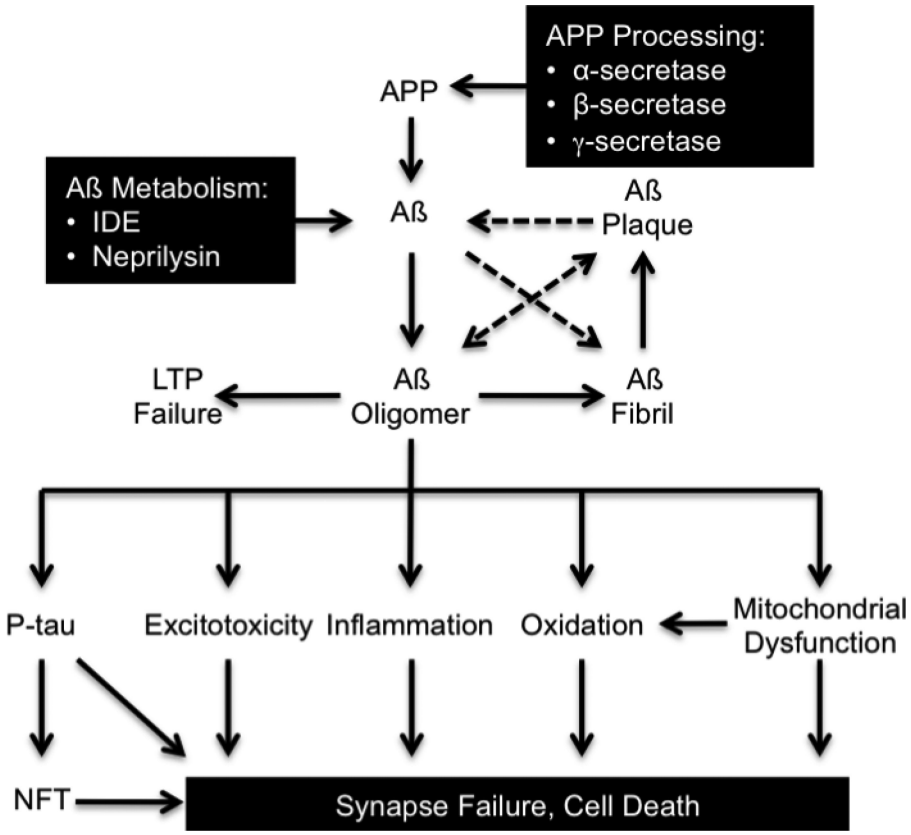

Figure.

Pathological cascade of AD. (Aß – amyloid beta protein; APP – amyloid precursor protein; IDE – insulin degrading enzyme; LTP – long term potentiation; NFT – neurofibrillary tangle; p-tau – phosphorylated tau protein).

Table 1

Possible Drue Targets for Symptomatic Therapies for AD

Acetylcholinesterase inhbition*
NMDA receptor modulation*
Nicotinic acetylcholine receptor activation
Gamma amino butyric acid receptor blockade
Serotonin receptor activation and blocade
Histamine H3 receptor blockade
Phosphodiesterase inhibition
Brain metabolism enhancement

* Targets for which FDA approved medications exist

Table 2

Possible Drue Targets for Disease-Modifying Therapies for AD

Aβ
Aβ Production
Alpha secretase enhancement
Beta secretase inhibition
Gamma secretase inhibition
Gamma secretase modulation
Aβ Degradation
Neprilysin activation
Insulin degrading enzyme activation
Aβ Removal
Vaccination
Passive immunization
Receptor-mediated removal from CNS
Prevent entry from periphery
Preventing Aβ Toxicity
Prevent aggregation by binding Aβ
Prevent oligomerization through metal protein attenuation
Tau
Prevent tau aggregation
Prevent tau hyperphosphorylation
Facilitate tau phosphatases
Microtubule stabilization
Neuroprotection
Ensure neuronal health with growth factor treatment or growth factor receptor activation
Prevent cell death with anti-apopotic agents
Ensure mitochondrial health
Block inflammatory disease processes

Table 3

AD Drug Candidates Currently in Phase III Trials*

Drug	Sponsor	Mechanism of Action
Bapineuzumab	Elan/Wyeth	Passive immunotherapy
Solanezumab	Eli Lilly	Passive immunotherapy
LY-450139	Eli Lilly	Gamma secretase inhibition
Dimebon	Medivation	Mitochondrial stabilization
Intravenous Immunoglobulin	Baxter	Passive immunotherapy

* Source: www.clinicaltrials.gov