



Emerging drug therapies for dementia are increasingly chosen to tackle molecular targets important in Alzheimer's disease (AD) pathobiology. Amyloid oligomers, amyloid deposits, and neurofibrillary tangles (NFTs) are characteristic findings in AD. Hence, drugs that interfere with these proteinaceous aggregates are receiving the most attention: a) alpha, beta, and gamma secretase modulators, b) inhibitors of amyloid beta (A β) aggregation, and c) anti-A β immunologic strategies.

Oxidative stress and inflammatory reactions appear part of a loop of neurotoxicity with the proteinaceous aggregates. Antioxidants and anti-inflammatory compounds have thus received much attention. Finally, other compounds may work by a variety of other mechanisms.

Key words: Alzheimer's disease, amyloid, secretase inhibitors, antioxidants, anti-inflammatory agents

Emerging Drug Therapies for Dementia

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the older adult. Hence, it has received the greatest attention in drug development. Fortunately, some of the advances in AD therapy may translate into benefits for other dementias as well. Therapies for AD currently approved by the Food and Drug Administration in the United States are symptomatic—that is, they help allay some of the symptoms of AD such as memory loss, other cognitive and behavioural changes, and impairment in activities of daily living. They have not been shown to alter the course of the illness. Numerous compounds with potential disease modifying effects are being investigated. Many of these compounds interfere with disease pathogenesis or progression. Some may have a neuroprotective effect that may delay onset of symptoms.

Current studies involve extension of uses of currently approved compounds, natural compounds, compounds approved for other medical conditions that may produce a benefit in AD, and novel compounds (Figure 1). To best understand emerging therapies for AD, it is easiest to subdivide them according to principal presumed target in AD: 1) amyloid beta (A β), 2) oxidative stress, 3) inflammation, and 4) other. Many have multiple modes of action.

Amyloid beta

Aberrant production and/or decreased clearance of A β peptides and hyperphosphorylated tau aggregates are widely accepted as implicated in AD pathogenesis. The severity of dementia inversely

correlates with measures of synaptic density. Soluble oligomers of A β are the earliest effectors of synaptic compromise in Alzheimer's disease.¹ There are three prominent amyloid-based therapeutic strategies: a) secretase modulation, b) inhibition of A β aggregation, and c) immunization against A β .

Secretase Modulation.

Three secretases (α , β , and γ) are involved in the sequential proteolytic processing of the amyloid precursor protein (APP). Alpha-secretase processing of APP occurs C-terminally of Lys16 in the A β sequence and thus precludes A β peptide generation. Soluble, nontoxic APP fragments are formed instead. Cleavage of APP by β - followed by γ -secretase results in toxic A β 40 and A β 42 fragments—the latter being more fibrillogenic and insoluble. Inhibition of the β - and γ -secretase targets is believed to have therapeutic potential.

Beta-secretase

Beta-secretase (or BACE, beta-site cleaving enzyme) is an aspartyl protease. Absence in knock-out mice shows minimal adverse effects,² but the properties of the active site of this enzyme make it difficult to find small-molecule inhibitors that cross the blood-brain barrier and bind with high affinity. In silico candidates (created by computer modeling) are emerging but are not yet in human trials.

Gamma-secretase inhibitors/modulators

Gamma-secretase inhibitors/modulators in clinical trials include LY450139 (phase II) and R-flurbiprofen (phase III). Early agents produced toxicity related to other

Key Points

Emerging drug therapies for dementia focus on Alzheimer's disease, the most common cause of dementia.

Current experimental treatments tackle specific pathways in disease pathogenesis and are expected to be protective rather than simply symptomatic.

The main targets of emerging drug therapies are 1) amyloid beta ($A\beta$), 2) oxidative stress, 3) inflammation, and 4) other (including neuroprotectants and metal chelators).

Drugs targeting $A\beta$ include β - and γ -secretase inhibitors, α -secretase modulators, amyloid disaggregants, and antibodies against $A\beta$.

substrates such as Notch. Newer agents are more specific inhibitors. LY450139 inhibits $A\beta$ formation in whole cell assays, transgenic mice, and beagle dogs. In normal human volunteers given doses ranging from 5–50 mg/day over 14 days, plasma $A\beta$ concentrations decreased up to 40% in a dose-dependent manner, but $A\beta$ concentrations were transiently increased afterwards. CSF $A\beta$ concentrations were unchanged. Adverse events were similar to placebo at doses of 40 mg/d or lower. At 50 mg/d, adverse events that were possibly drug-related were noted.³

A subset of NSAIDs such as ibuprofen, indomethacin, and flurbiprofen may have direct $A\beta$ -lowering properties in cell cultures as well as transgenic models of AD-like amyloidosis.⁴ R-flurbiprofen, an enantiomer lacking Cox-inhibitory activity and related gastric toxicity, is safe and well tolerated in healthy older volunteers at doses up to 1,600 mg/d. In a one-year phase II study of 207 subjects with mild-to-moderate AD receiving 400 mg b.i.d., 800 mg b.i.d., or placebo, statistical significance was not reached in memory measures. A subset of mild patients on the highest dose, however, who developed high levels of the drug in their bloodstream had significant benefits in activities of daily living and overall function. A phase III trial with similar dosing but longer duration is in progress.

Glycogen synthase kinase-3 (GSK-3) is required for maximal processing of APP. It also phosphorylates tau protein. GSK-3b inhibitors such as lithium, valproate, or docosahexaenoic acid (DHA)

reduce tau phosphorylation and modulate γ -secretase activity, reducing A, production *in vitro* and *in vivo*.

Lithium or valproate, at therapeutic levels, may inhibit γ -secretase, and lithium reduces $A\beta$ 40 and $A\beta$ 42 levels in transfected Chinese hamster ovary (CHO)-cells, in primary neurons, and in mouse brain *in vivo*.⁵ Valproate protects cultured rat hippocampal neurons against $A\beta$ - and glutamate-induced injury. The Alzheimer's Disease Cooperative Study (ADCS), a study group funded by the National Institute on Aging (NIA), is conducting a phase III study of valproate in Dementia (VALID).

Alpha-cleavage

Alpha-cleavage of APP is beneficial. Rasagiline (N-propargyl-1R-aminoidan), a novel, highly potent, irreversible monoamine oxidase (MAO) B inhibitor, processes APP to the neuroprotective-neurotrophic soluble APP alpha (sAPP α) by PKC (protein kinase C) and MAP (mitogen-activated protein) kinase-dependent activation of alpha-secretase.⁶ Promoting soluble, nonamyloidogenic APP cleavage may be another strategy to treat AD.

Secretases are embedded in the cell membrane. APP cleavage by secretases occurs predominantly in post-Golgi secretory and endocytic compartments and is influenced by cholesterol, indicating a role of membrane lipid composition in proteolytic processing of the beta-amyloid precursor protein. Statins influence APP processing in neurons and reduce amyloid-induced inflammation in glia.⁸ Epi-

demologic studies largely suggest that 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) may reduce the risk for Alzheimer's disease.⁷ The Cardiovascular Health Cognition study produced mixed results depending on how the data was looked at.⁹ This emphasizes the importance and need of prospective, randomized, placebo-controlled trials. A one-year controlled phase II study of atorvastatin 80 mg/d in 98 patients, mean age 78.5 years, with mild-to-moderate AD revealed marginally significant differences for the Clinical Global Impression of Change (CGIC) and for the Alzheimer's Disease Assessment Scale–Cognitive subtest (ADAS-Cog) when results were measured by repeated measures ANCOVA (P values 0.07 and 0.055, respectively). Regression analysis indicated a change in the slope of deterioration on the Mini-Mental Status Exam (MMSE).¹⁰ Phase III trials of simvastatin and of atorvastatin are underway. Other cholesterol-lowering agents, such as the acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitor, CP-113,818, may also reduce amyloid pathology.¹¹

Inhibition of $A\beta$ Aggregation.

Resveratrol (trans-3,4',5-trihydroxystilbene), a naturally occurring polyphenol mainly found in grapes and red wine, markedly lowers levels of secreted and intracellular $A\beta$ peptides produced from different cell lines. Resveratrol promotes a proteasome-dependent intracellular degradation of $A\beta$.¹² Other polyphenolic antioxidants, including green tea catechins and curcumin, have potential as protective factors for several diseases of aging, including AD. Catechins seem to reduce $A\beta$ production, while curcumin limits $A\beta$ aggregation and resveratrol may be particularly useful in protecting DNA via sirtuin.

NC-758 (3-amino-1-propanesulfonic acid; AlzhemedTM) is a GAG-mimetic molecule that inhibits fibrillization and promotes clearance of amyloid fragments. In a Phase II study, 58 subjects with mild-to-moderate AD were divided into four groups—placebo, 50 mg b.i.d., 100 mg b.i.d., and 150 mg b.i.d.—and

treated for 12 weeks. Results showed a dose-dependent cerebrospinal fluid A β reduction. In the subset of mild AD patients who received the highest dose for 20 months, average scores on cognitive tests remained improved for the duration, per the manufacturer's data.¹³ A phase III trial is underway.

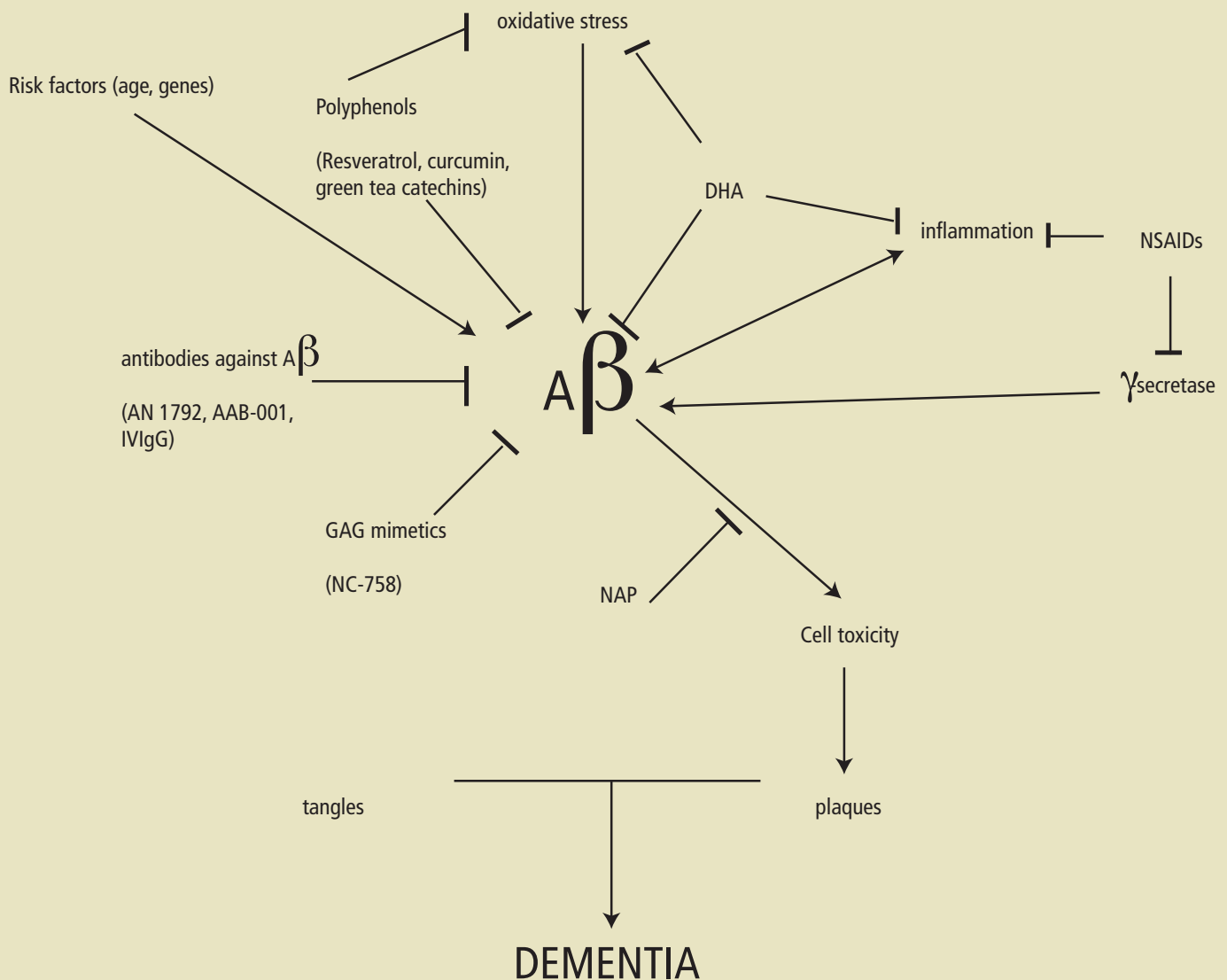
Immunization against A β

In animal models, A β immunotherapy not only reduces amyloid, amyloid-associated gliosis, and neuritic dystrophy, but

leads to clearance of early hyperphosphorylated tau aggregates, which are another pathological hallmark of AD.¹⁴ Amyloid beta immunization results in alleviation of memory impairment in transgenic mice. In humans, active vaccination results in a trend toward cognitive benefit in antibody responders. Surprisingly, responders show an increased rate of hippocampal atrophy by MRI. Several autopsies showed plaque clearance.¹⁵ The phase II trial of vaccination with the synthetic A β

(AN1792; AIP-001) was halted early because of encephalitis, presumably induced by T-cell immune responses, in 6% of subjects. To avoid the complication of encephalitis, current strategies involve passive immunotherapy. Humanized monoclonal anti-amyloid antibody is under development by a number of companies. There is evidence that anti-A β antibodies could bind and help clear soluble oligomers of A β distinct from microglial-mediated clearance and peripheral sink effects, but adequately to

Figure 1: Emerging Drug Therapies for Dementia



A β =amyloid beta, DHA=docosahexaenoic acid, NSAIDs=Nonsteroidal anti-inflammatory agents, IVIgG=intravenous immunoglobulin, NAP=NAPVSIPQ, a short octapeptide. Arrows=promoting effect, bar lines=inhibiting effect.

reduce concentrations toxic to synaptic physiology.¹⁶ Elan's humanized monoclonal antibody (AAB-001) is designed to provide antibodies to beta amyloid directly to the patient, thus obviating the need for an immune response by the patient. It has entered phase II testing.

Another immunologic strategy involves intravenous immunoglobulin (IVIgG) which contains antibodies against A β . These antibodies selectively target A β and are capable of antagonizing the potential neurotoxic effects of A β as well as its fibrillization—the prerequisite for plaque formation. In a preliminary open-label trial, five patients with AD were given IVIgG 0.4 g/kg body weight on three consecutive days every four weeks for six months. Serum and CSF A β 42 levels were not significantly changed. Total A β in the CSF decreased by 30% while total serum A β increased by 233%, suggesting peripheral sequestration. An improvement of 3.7 points was detected on the ADAS-Cog.¹⁷ A larger follow-up study is expected.

Oxidative Stress

A large body of evidence implicates oxidative damage in AD pathogenesis. Oxidative damage is possibly the earliest event in AD, based on postmortem studies showing increases in neuronal 8OHdG (8-hydroxy-2'-deoxyguanosine) and 3-nitrotyrosine which precede A β plaques and NFTs. There is approximately a two-fold increase in DNA damage in lymphocytes of patients with Mild Cognitive Impairment (MCI; a strong risk for developing AD) and AD.¹⁸

Toxic soluble A β oligomers appear to have synaptic receptors colocalizing with PSD-95 (postsynaptic density protein 95), and A β 42 accumulates in dendrites in AD patients where it may cause oxidative damage and caspase activation. Caspases are a family of proteins that are one of the main effectors of apoptosis. Developmentally regulated brain protein (drebrin), a dendritic spine actin-regulated protein, shows major (70–97%) losses in AD. Postsynaptic actin-rich dendritic spines are dynamically involved in synaptic plasticity, learning, and memo-

ry. Docosahexaenoic acid (DHA), an essential omega-3 polyunsaturated fatty acid, is a major component of neuronal membrane phospholipids. It is enriched in synapses and central to postsynaptic signalling and neuroprotection. DHA promotes neuronal survival by facilitating membrane translocation/activation of Akt through its capacity to increase phosphatidylserine (PS), the major acidic phospholipid in cell membranes. In vivo reduction of DHA by dietary depletion of n-3 fatty acids decreases hippocampal PS and increases neuronal susceptibility to apoptosis in cultures.¹⁹ Drebrin is markedly decreased by n-3 PFA depletion in transgenic [Tg2576; Tg(+)] mice. Even short-term DHA restriction in Tg(+) mice leads to significant postsynaptic protein losses that correspond to a memory acquisition deficit on Morris water maze hidden platform testing. DHA supplementation corrects acquisition, but not retention deficits. DHA reduces amyloid accumulation even when begun in old mice with high amyloid.

DHA is reduced in AD. Epidemiological studies suggest that diets high in DHA are protective against AD. Deficits in DHA appear to contribute to insulin resistance, loss of p85 subunit, and adult-onset diabetes and may be a link in the increased risk of AD in diabetics. US intake of n-3 PFAs is estimated at 57–70 mg/day versus the recommended 200–300 mg/d. DHA-deficient diet may be a readily alterable environmental risk factor for AD.

Curcumin (diferuloylmethane), a polyphenol, is a component of the culinary spice turmeric used in curry powder. It has antioxidant, anti-inflammatory, and anti-amyloid activity. It can suppress Tumour Necrosis Factor (TNF)-induced NF- κ B (nuclear factor- κ B) and hence may have a role in cancer therapy. It is being tested in multiple studies as a chemotherapeutic or chemopreventative because it can suppress cellular transformation, proliferation, invasion, angiogenesis, and metastasis. It has multiple properties that make it attractive as a potential agent against AD. It is antioxidant. It inhibits brain lipid peroxidation

five- to ten-fold better than vitamin E. It also has anti-inflammatory properties, inhibits prion protein, prevents fibril formation, inhibits oligomer formation and A β aggregation, lowers total cholesterol, raises HDL, chelates metal (iron), and extends life in mice. Curcumin stimulates murine microglial phagocytosis of plaques in human AD sections, increases microglial staining associated with plaque, and reduces total A β . Curcumin is also synergistic with n-3 PFAs. It has a favourable toxicity profile. No dose-limiting toxicity was noted in doses up to 10 g/day in human volunteers.²¹ A phase II study is underway.²² Dose and duration required for a beneficial effect are unknown. CNS penetration is unknown. Blood levels in persons receiving 500–2000 mg doses are barely detectable. At two hours after an 8000 mg dose, peak blood levels of 1.77 micromoles are observed. The study aims to determine the safety and tolerability of 2000 mg and 4000 mg/day of curcumin C3 Complex versus placebo over a period of six months.

In a placebo-controlled two-year study of vitamin E (2,000 IU/d), functional deterioration slowed and nursing home placement was delayed in patients with moderate AD.²³ However, in the HOPE-TOO meta-analysis study, risk of heart failure increased on vitamin E 400 IU/d. Such a side-effect increase was absent in the Alzheimer study above that did not involve cardiac patients. Vitamin E alone may not provide the spectrum of antioxidant benefit needed to significantly affect AD. A clinical study involving vitamin E, vitamin C, alpha-lipoic acid, and coenzyme Q is underway.

Inflammation

A large number of factors known to be major participants in inflammatory processes are present in AD.²⁴ It is believed the inflammatory response is secondary to senile plaques (SPs) and NFTs that, in turn, trigger the formation of more SPs and NFTs in a self-sustaining destructive cycle. NSAIDs are neuroprotective against amyloid toxicity in vitro and in vivo. Epidemiological studies show that

NSAIDs may delay or slow progression of AD. However, results of AD trials have been disappointing. Anti-inflammatory agents tested prospectively include prednisone, hydroxychloroquine, acetylsalicylic acid, naproxen, rofecoxib, and celecoxib. Indomethacin and diclofenac had high dropout rates.³ More recently, enthusiasm for NSAIDs has been further tempered by reports of increased risk of cardiac complications. It appears that if any NSAID proves effective it will not be related to anti-inflammatory activity but to antisecretase activity.

Other

Zinc, copper, and iron are present in amyloid plaques. Zinc and copper precipitate A β rapidly and reversibly. Copper deprivation strongly down-regulates APP gene expression and reduces APP levels. Clioquinol, a Cu and Zn chelator, elevates soluble brain A β and inhibits A β deposition. In a phase II trial, clioquinol inhibited cognitive decline and decreased plasma A β 42 levels in moderate-to-severe AD. Drug impurity in the production process led to discontinuation of a phase II/III clinical trial.

Activity-dependent neuroprotective protein (ADNP)—a glial-derived neurotrophin—contains a peptide, NAP, which is an exceedingly potent peptide neuroprotectant effective in nanomolar concentrations. NAP is highly effective against a variety of models of amyloid toxicity. Human studies are needed.

Future Developments

One may expect steady progress in various anti-amyloid therapeutic strategies. It is conceivable that a number of therapies will be approved within a matter of three to five years. The most promising therapies at present are NC-758, R-flurbiprofen, and passive immunotherapy.

Conclusion

Research on drug therapies for Alzheimer's disease is enjoying a boom. Literally dozens of compounds are in various stages of testing. Heretofore, drug therapy for AD has been symptomatic. Many emerging therapies are

anticipated to have disease-modifying effects. Compounds under investigation tackle different pathways in the disease process. Hence, some may be complementary, others may work best for prevention rather than treatment once the disease has set in, and yet others may work under select conditions. To understand the various potential treatments for AD, it is easiest to classify them according to proposed target in disease pathogenesis.



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