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Frontiers in Alzheimer's Disease Therapeutics

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Abstract

Alzheimer disease (AD) is a progressive neurodegenerative disease which begins with insidious deterioration of higher cognition and progresses to severe dementia. Clinical symptoms typically involve impairment of memory and at least one other cognitive domain. Because of the exponential increase in the incidence of AD with age, the aging population across the world has seen a congruous increase AD, emphasizing the importance of disease altering therapy. Current therapeutics on the market, including cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists, provide symptomatic relief but do not alter progression of the disease. Therefore, progress in the areas of prevention and disease modification may be of critical interest. In this review, we summarize novel AD therapeutics that are currently being explored, and also mechanisms of action of specific drugs within the context of current knowledge of AD pathologic pathways.

Keywords

Alzheimer disease; amyloid; antioxidants; cholinesterase inhibitors; luteinizing hormone; mitochondrial therapy; neurodegenerative drugs; NMDA antagonists; tau

INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative disease that initially presents clinically with an insidious impairment of cognitive function, and within 5–10 years results in debilitation, often encompassing severe memory loss, confusion, behavior and personality changes, speech dysfunction, an inability to live independently, and ultimately a near vegetative state. Death from pneumonia is typical [Smith, 1998]. As the most common cause of dementia in the elderly, AD is an increasingly problematic medical, economic, and social threat to societies with growing elderly populations. Strongly correlated with age, the incidence of

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Conflict of Interest Statement

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AD is 1% for those 60 years of age or less, and roughly doubles every 5 years thereafter [Ziegler-Graham *et al.*, 2008]. Considering prevalence, 4 million people are currently afflicted with AD in the United States and the elderly population is growing precipitously [Qiu *et al.*, 2007]. Current estimates for the year 2050 place the number of people in the United States suffering from AD at approximately 16 million [Brookmeyer *et al.*, 2007].

Although presentation of clinical symptoms may differ significantly between individuals, accurate diagnosis is made in 80–90% of cases and is based on clinical assessment paired with continuously improving radiologic techniques. Microscopically, AD is characterized by several hallmark pathological lesions, namely: neuritic plaques, neurofibrillary tangles (NFTs), neuropil threads, and diffuse plaques [Kaminsky *et al.*, 2010]. NFTs are filamentous aggregates of hyperphosphorylated tau protein which encircle or displace the neuronal nucleus; the intracellular, insoluble lesions are highly resistant to cellular clearance *in vivo*. Neuritic plaques, conversely, are found extracellularly and are composed primarily of aggregated amyloid- β (A β) protein. Though plaques and tangles have long been seen as the characteristic pathological structures of AD, they are no longer considered the primary progenitors of the disease pathway, but instead are viewed as downstream sequelae of prior cellular insults [Smith *et al.*, 2000, Zhu *et al.*, 2007]. Alternatively, oxidative stress and dysfunction of mitochondrial dynamics are now considered two primary role-players in the early pathological cascade [Zhu *et al.*, 2001, Petersen *et al.*, 2007, Wang *et al.*, 2009, Smith *et al.*, 2010]. If early oxidative stress and mitochondrial dysfunction are allowed to proceed unabated, secretion and aggregation of A β and NFTs, as well as microglial and astrocytic activation, neuroinflammation, and cell cycle aberration soon follow [Zhu *et al.*, 2004, Mancuso *et al.*, 2008, Bonda *et al.*, 2009, Bonda *et al.*, 2010]. As such, additional components of neuritic plaques include pro-inflammatory cytokines, apolipoproteins, α 1-antichymotrypsin, and various constituents of the complement cascade. While the precise role of senile plaques and NFTs in the pathologic progression of AD is contentious and the subject of ongoing research [Castellani *et al.*, 2008, Castellani *et al.*, 2009], pathological changes ultimately result in neuronal death first evident in the entorhinal cortex, then the hippocampus and isocortex, and finally the neocortex [Burns *et al.*, 1997, Whitehouse, 2006].

Because of the loss of cortical neurons and cholinergic function in AD, initial therapeutic research targeted cholinergic deficiency [Farlow *et al.*, 1998]. Consequently, cholinesterase inhibitors (ChEIs) were the first pharmaceutical agents approved in the treatment of AD [Moreira *et al.*, 2006]. This strategy, although valuable in mild to moderate cases, only provides symptomatic relief and does not alter disease progression [Giacobini, 2000; 2001; 2002]. In addition to ChEIs, the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine is the only additional drug currently approved by the FDA for treatment in AD and is indicated in moderate to severe cases [Kornhuber *et al.*, 1989]. Over-activation of NMDA receptors by excess synaptic glutamate is thought to lead to neuronal death through excitotoxicity. Similar to ChEIs, memantine shows some symptomatic benefit [Mcshane *et al.*, 2006, Van Dyck *et al.*, 2007]. Given the paucity and ineffectiveness of symptomatic treatments, novel methods of AD treatment are increasingly being pursued and span from modifying disease specific protein targets to additions to the diet including fish oil or pharmacologically created medical food supplements (Figure 1).

In addition to symptomatic treatments, novel drug development includes an emphasis on prevention of primary cellular insults which initiate AD, and intervention measures which modulate the neurotoxic pathways once in motion. As such, this paper will review therapeutic interventions under current investigation divided among three categories: preventative, disease-modifying, and symptomatic treatment. Since the AD pathological pathway is multifactorial involving a host of genetic, environmental, and behavioral

components, *potential* therapeutic targets are numerous [Shah *et al.*, 2008], leaving some room for cautious optimism (Figure 1).

PREVENTATIVE APPROACHES

Given the lack of current pharmacological options that target primary disease process, and the probable advanced nature of the disease when clinically symptomatic [Castellani *et al.*, 2001, Su *et al.*, 2010], a preventative approach appears to have some merit. Estimates in fact suggest if therapeutic interventions delay disease onset by a even one year, approximately 9.2 million fewer cases of AD would be observed in 2050 than expected [Brookmeyer *et al.*, 2007]. Despite logistical difficulties in research, several large clinical studies focusing on preventative strategies such as antioxidant therapy, protection of mitochondrial dynamics, use of cholesterol lowering drugs, and anti-inflammatory treatment have noteworthy findings.

Antioxidant Therapy

Recent evidence suggests oxidative stress plays an early and active role in the AD pathological cascade [Zhu *et al.*, 2007]. Reactive oxygen species (ROS), such as the highly reactive molecules superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^{\bullet}) are naturally created in the mitochondria as the cell generates ATP through cellular respiration [Petersen *et al.*, 2007]. Although the cell has defensive machinery to reduce ROS such as the enzymes superoxide dismutase and catalase, some ROS inevitably leak from mitochondria and damage literally every cellular component including phospholipids, proteins, and notably, mitochondrial DNA (mtDNA) [Ansari *et al.*, 2010]. As ROS damage shows an increased incidence in AD and occurs temporally early in the initiation of the disease [Zhu *et al.*, 2001, Zhu *et al.*, 2004], antioxidant therapy may present a valuable preventative strategy [Liu *et al.*, 2007, Aliev *et al.*, 2008].

Readily available through dietary supplementation, naturally occurring antioxidants, such as several vitamin moieties, present an ideal preventative measure. Evidence of protection from AD by supplements such as antioxidant vitamins (E, C, and carotenoids) and B vitamins (B6, B12, and folate) is inconsistent [Perrig *et al.*, 1997, Gillette Guyonnet *et al.*, 2007, Middleton *et al.*, 2009]. However, several large longitudinal studies found folate supplementation is associated with a reduced risk of AD [Corrada *et al.*, 2005], combination therapy with vitamins E and C is associated with reduced incidence and prevalence of AD [Zandi *et al.*, 2004], and treatment with vitamin E may slow the progression of AD [Sano *et al.*, 1997]. Additional studies which control carefully for confounding factors are certainly warranted in the case of antioxidant vitamin protection.

In addition to naturally occurring antioxidant vitamins, several other drugs are under investigation for the prevention of ROS based damage. As mitochondria are the principal producers of ROS [Lee *et al.*, 2004] and mitochondrial components undergo the initial oxidative insults temporally [Ogawa *et al.*, 2002, Aliev *et al.*, 2003, Zhu *et al.*, 2004, Zhu *et al.*, 2006], mitochondrial antioxidant pharmaceuticals present a promising target for therapeutic development. One such therapy in development involves treatment with Coenzyme Q₁₀ (CoQ₁₀), the protein responsible for carrying high energy electrons from complex I and complex II in the electron transport chain (ETC) through subsequent oxidation and reduction. Studies show potential neuroprotective effects of CoQ₁₀ including the suppression of toxic free radical production, reduction of ROS injury, and stabilization of mitochondrial function [Beal, 2004, Wadsworth *et al.*, 2008, Lee *et al.*, 2009]. Despite positive study results, CoQ₁₀ treatment presents important obstacles. Firstly, proper functioning of CoQ₁₀ within the cellular respiration pathway requires an intact and fully functional ETC. Oxidatively damaged mitochondria, observed early in AD, often do not

contain intact ETCs as many enzymes involved with oxidative phosphorylation become irreversibly damaged; thus, CoQ₁₀ administration to cells with mitochondria exhibiting early stages of dysfunction is ineffective [Lass *et al.*, 1999]. In addition, oral administration of CoQ₁₀ did not significantly increase the protein levels of CoQ₁₀ in the brain [Kwong *et al.*, 2002]. This finding suggests that the current formulation of CoQ₁₀ lacks the ability to penetrate the blood brain barrier (BBB). Due to the drawbacks of CoQ₁₀ therapy, other moieties, which possess greater BBB permeability and do not require an intact ETC for proper functioning, are under investigation.

One such formulation is a triphenylphosphonium-linked ubiquinone derivative known as MitoQ [Murphy, 2001]. Like CoQ₁₀, MitoQ is shown to inhibit ROS production, protect mitochondrial oxidative phosphorylation, preserve mitochondrial structural integrity, and ultimately prevent cell death [Murphy *et al.*, 2007]. In addition, MitoQ addresses the shortcomings of CoQ₁₀; MitoQ is shown to effectively operate in the absence of an intact ETC [Lu *et al.*, 2008] and concentrate several hundred-fold in mitochondria [Smith *et al.*, 2004]. At this time, MitoQ remains on the horizon for AD treatment as the therapy was found to be effective in Phase II clinical trials for liver damage associated with HCV infection.

Additional antioxidants under investigation for future treatment of AD include acetyl-L-carnitine (ALCAR) and R- α -lipoic acid (LA). Differing combinations of these two antioxidants are shown to reduce cellular insults by ROS, and in particular, prevent mitochondrial abnormalities in mouse models of AD [Siedlak *et al.*, 2009], and prevent cognitive decline and/or restore cognitive functioning in aged rats and dogs [Liu *et al.*, 2002, Liu *et al.*, 2002, Liu *et al.*, 2002, Ames *et al.*, 2004, Milgram *et al.*, 2007, Long *et al.*, 2009]. Notably, mitochondrial structural integrity was preserved and the number of mitochondria increased in the hippocampal region by ALCAR/LA administration [Aliev *et al.*, 2009]. While much investigation remains to be completed regarding the role antioxidants may or may not play in AD treatment, the above mentioned therapies under current investigation present exciting possibilities.

Anti-inflammatory Therapy

Although the precise role of inflammatory processes in AD pathogenesis remains elusive, several *in vitro* and *in vivo* animal and human studies implicate neuroinflammation in disease progression [Kalaria, 1999, Moore *et al.*, 2002]. In particular, activated microglia, the resident guardian macrophages of the central nervous system (CNS), and reactive astrocytes, the most abundant CNS cells responsible for a multitude of critical functions including buffering of extracellular environment, preservation of the BBB, and generation of energy substrates, are directly involved in neuroinflammation. In the presence of an inflammatory stimulus, reactive astrocytes and activated microglia express and/or secrete increased concentrations of cytokines, chemokines, ROS, growth factors, major histocompatibility complex type II, and complement proteins: all pro-inflammatory mediators. In relation to AD, human post-mortem studies and transgenic (Tg) animal models of AD show neuritic plaque development associated with glial activation [Apelt *et al.*, 2001, Wegiel *et al.*, 2001], suggest microglia assist in conversion of A β to its fibrillar form, induce diffuse plaques to aggregate into neuritic plaques [Griffin *et al.*, 1995, Mackenzie *et al.*, 1995, Cotman *et al.*, 1996, Sasaki *et al.*, 1997], and induce glutamate release contributing to excitotoxicity [Piani *et al.*, 1992]. Due to an increasing body of research suggesting a progenitive role of neuroinflammation in AD, several anti-inflammatory therapies have been studied.

Notably, several large longitudinal studies show use of anti-inflammatory drugs are associated with a lower incidence of AD [In T' Veld *et al.*, 2001, Lindsay *et al.*, 2002,

Cornelius *et al.*, 2004]. In particular, findings show non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) protect against the development of AD [McGeer *et al.*, 1996, Etminan *et al.*, 2003], increased duration of NSAID use is associated with a lower relative risk for AD [Stewart *et al.*, 1997], and naproxen in particular has a positive preventative effect [Cole *et al.*, 2010]. Importantly, although anti-inflammatory administration shows preventative potential, several studies show treatment of patients with clinically diagnosed mild to moderate AD has no effect [Aisen *et al.*, 2000, Van Gool *et al.*, 2001, Aisen *et al.*, 2003, Reines *et al.*, 2004]. This lends further support that once early pathological pathways, including neuroinflammation, initiate, preventative strategies quickly become futile.

DISEASE-MODIFYING APPROACHES

While preventing the onset of AD entirely is an ideal aim, the multitude of factors influencing the onset and progression of AD as well as poorly understood nature of the primary pathogenic processes and outright misconceptions inherent in leading hypotheses, make prevention unlikely; therefore, therapies that blunt the secondary effects of established disease are in high demand for both current and future AD patients.

Stabilization of Mitochondrial Dynamics

One such critical secondary cellular insult is disruption of mitochondrial function. Mitochondria are highly dynamic organelles which constantly fuse and divide within cells in response to energy demands [Chan, 2006]. Given 95% of the cell's energy is provided by the citric acid (TCA) cycle and oxidative phosphorylation of mitochondria, and neurons have extremely high metabolic demands, proper functioning of mitochondria is absolutely critical to neuronal viability. As mentioned prior, the integrity of mitochondrial structure and utility are significantly compromised in AD [Hirai *et al.*, 2001, Wang *et al.*, 2008, Wang *et al.*, 2008]; mitochondria, therefore, present a valuable potential target for modulation of AD.

Besides the prior mentioned mitochondrial antioxidants, Dimebon is believed to target mitochondrial dysfunction in AD. Specifically, evidence indicates Dimebon binds to and blocks the mitochondrial permeability pore (MPP) [Bachurin *et al.*, 2003]. The MPP is a multiprotein complex involving both the inner and outer mitochondrial membranes which serves to regulate the transfer of ions and proteins in and out of mitochondria with particular focus on maintaining intracellular Ca^{2+} homeostasis. Early in the pathological pathway of AD, oxidative stress and other neurotoxic insults can irreversibly open the MPP eliciting significant cellular stress [Parks *et al.*, 2001]. Through closure of faulty MPPs, Dimebon may serve as a potent neuroprotector. Importantly, although Dimebon showed unprecedented success in an initial relatively small Phase II trial in patients with mild-to-moderate AD [Doody *et al.*, 2008], a recently completed double-blind large-scale Phase III clinical trial indicated a discouraging similarity in cognitive outcomes between Dimebon and control groups. While the fate of Dimebon is yet to be determined, the strategy of attenuating mitochondrial dysfunction in AD will certainly continue to be the subject of much future inquiry.

Cessation of Luteinizing Hormone Expression

Dyshomeostasis of hormones, luteinizing hormone (LH) in particular, appears to play a significant role in AD. Substantiating this assertion, the incidence of AD in women, who experience severe hypothalamic-pituitary-gonadal hormone changes with menopause particularly an elevation of circulating LH, is approximately two times higher than men [Jorm *et al.*, 1998]. Evaluation of patients with Down's syndrome (DS) lend further evidence supporting the role of LH in AD. Men with DS are twice as likely as women with DS to develop AD, showing the reverse trend of the normal population [Bonda *et al.*, 2010].

Demonstrating the same phenomenon as post-menopausal women, men with DS have elevated levels of circulating LH suggesting a direct link between risk for AD and LH level [Casadesus *et al.*, 2006, Webber *et al.*, 2007]. In fact, elevated LH is the only hormonal similarity discovered to date which connects the predisposition to AD observed in normal women and men with DS. Many recent investigations have, therefore, been launched into the role of LH in AD and the evaluation of LH-based treatments.

In short, patients afflicted with AD show serum concentrations of LH approximately twice as high as age-matched controls [Bowen *et al.*, 2000, Short *et al.*, 2001] elevated LH is observed in the AD vulnerable hippocampus [Bowen *et al.*, 2002], and LH appears to encourage A β deposition into senile plaques [Bowen *et al.*, 2004, Webber *et al.*, 2007]. A breakthrough on the treatment front, the novel therapeutic leuprolide acetate is shown to reduce LH levels by downregulating the expression of gonadotropin releasing hormone (GnRH) receptor levels in the anterior pituitary [Marlatt *et al.*, 2005]. This appears to have a significant positive effect in AD as leuprolide acetate reduces A β deposition in rats [Okada *et al.*, 1996], and modulates cognition in amyloid- β protein precursor (A β PP) overexpressing Tg mice and humans [Casadesus *et al.*, 2006] [NCT00076440]. In addition, high doses of leuprolide acetate attenuated cognitive decline (ADCS-CGIC, ADAS-Cog) and stabilized activities of daily living (ADCS-ADL) in Phase II clinical trials of patients with mild to moderate AD [<http://www.secinfo.com/d14D5a.z6483.htm>, pp. 56–64]. Though much study is still required, LH ablating therapies are quite promising as a novel treatment avenue.

Tau-focused Therapies

As tau hyperphosphorylation and aggregation into pathological NFTs is a significant aspect in the development of AD, tau-focused therapeutic advancement is of much current interest. Notably, the abundance of NFTs in AD vulnerable brain regions is correlated with cognitive decline [Castellani *et al.*, 2006, Nunomura *et al.*, 2006], and NFT accumulation is therefore used to definitively diagnose AD postmortem [Perry *et al.*, 1985]. Consequently, targeting tau to inhibit NFT build-up or encourage NFT degradation may prove to be an important therapeutic strategy.

Inhibition of tau hyperphosphorylation—Evidence suggests the hyperphosphorylation of tau precedes NFT formation. Therefore, the strategy of inhibiting tau phosphorylation is under investigation as a potential AD modulating therapy. In particular, tau phosphorylation at threonine 231, and serines 235 and 262 appears to be responsible for the fibrillization and aggregation that produces NFTs. Glycogen synthase kinase 3 (GSK3) is believed to be the primary kinase which induces the hyperphosphorylation of tau [Shiurba *et al.*, 1996] as it is shown to co-localize to NFTs in AD vulnerable neurons [Imahori *et al.*, 1997], and Tg mice engineered to overexpress GSK3 show increased tau hyperphosphorylation and AD symptomology [Lucas *et al.*, 2001, Hernandez *et al.*, 2002]. Hence, several therapeutic agents aimed at inhibiting GSK3 are in early stages of development and show promising initial results. In this regard, administration of the GSK3 inhibitor LiCl to tau overexpressing Tg mice prevented the development of NFTs [Engel *et al.*, 2006], reduced tau phosphorylation [Noble *et al.*, 2005], and reduced concentration of insoluble tau [Perez *et al.*, 2003]. In addition, other GSK3 inhibitors SB216763 and CHIR-98014 [Selenica *et al.*, 2007], as well as a non-specific kinase inhibitor SRN-003-556 [Hampel *et al.*, 2009] are under early investigation for efficacy in AD treatment.

Besides preventing tau phosphorylation by direct inhibition of tau kinases, another strategy under inquiry is the inhibition of the β -N-acetylglucosamine (O-GlcNAc) cleaving enzyme O-GlcNAcase. Tau is shown to be postrationally glycosylated with O-GlcNAc at the

same threonine and serine residues that become pathologically phosphorylated. Consequently, O-GlcNAc glycosylation acts as a competitive inhibitor to tau hyperphosphorylation and subsequent aggregation into NFTs [Lefebvre *et al.*, 2003, Liu *et al.*, 2004], so preventing the cleavage of O-GlcNAc may therefore be a valuable strategy. In this regard, thiamet-G, a potent O-GlcNAcase inhibitor, induced a reduction of tau phosphorylation at threonine 231, and serines 396 and 404 in rats [Liu *et al.*, 2004]. Although the molecules under current investigation which seek to inhibit tau hyperphosphorylation are in early stages and many obstacles still must be addressed, tau phosphorylation as a target in AD treatment remains valid nonetheless.

Inhibition of tau oligomerization and fibrillization—Following tau hyperphosphorylation, monomeric tau begins to aggregate into oligomers which proceed to further accumulate into fibrils. Therefore, in lieu of hyperphosphorylation inhibition, another potential strategy seeks to prevent formation of toxic oligomers and fibrils [Brunden *et al.*, 2009, Brunden *et al.*, 2010]. Closest to the therapeutic market in this category, methylene blue, a histologic dye, recently completed a Phase II clinical trial with positive results and will begin Phase III trials soon [Neugroschl *et al.*, 2009]. Several additional tau aggregation inhibitors are under preclinical research as well and show promise for the future [Pickhardt *et al.*, 2005, Larbig *et al.*, 2007, Crowe *et al.*, 2009].

Degradation of hyperphosphorylated tau—In addition to the prevention of hyperphosphorylation and aggregation of tau, an additional strategy aimed at ameliorating presumed toxic deposition of phosphorylated tau is to increase its intracellular degradation through the ubiquitin proteasome system [Brunden *et al.*, 2009]. Evidence suggests this may be accomplished through the inhibition of heat shock protein 90 (HSP90). HSP90 serves to refold denatured proteins and its inhibition is believed to attenuate the preservation of phosphorylated tau, therefore enhancing its degradation [Zhang *et al.*, 2004, Dickey *et al.*, 2007]. Notably, the HSP90 inhibitor EC102 reduced the amount of hyperphosphorylated tau in the brains of Tg mice engineered to overexpress tau [Luo *et al.*, 2007] and efficiently inhibited HSP90 in human cortical AD homogenates at 1000-fold lower concentrations than control homogenates [Dickey *et al.*, 2007] indicating a clinically safe dosing range is available. It is important to note that the ubiquitin proteasome degradation system involves the precise threading of a denatured peptide through the small opening of the cylindrical proteasome. Therefore, once hyperphosphorylated tau becomes fibrillized, it no longer is an available target for this system being too wide to enter the proteasome. Nevertheless, tau degradation remains an exciting and promising strategy in the modification and attenuation of destructive AD pathology.

Amyloid-focused Therapy

Along with hyperphosphorylated tau tangles, A β plaques compose the second hallmark pathological marker of AD. Notably, increasing evidence indicates A β may actually be a protective measure used by the cell to attenuate damage by oxidative stress [Zhu *et al.*, 2001, Zhu *et al.*, 2007], as A β has antioxidant properties [Cuajungco *et al.*, 2000, Kontush, 2001, Kontush *et al.*, 2001, Rottkamp *et al.*, 2001, Hayashi *et al.*, 2007, Nakamura *et al.*, 2007], and the appearance of mitochondrial abnormalities and ROS precedes that of A β deposition [Petersen *et al.*, 2007]. However, the possibility that oversecretion of A β , (perhaps caused by oxidative stress) and eventual A β aggregation into senile plaques, is a toxic event is implicit in the literature even though somewhat dated in recent studies focusing on soluble oligomeric species. Hence, current amyloid-focused treatment strategies in development aim to prevent the accumulation and aggregation of insoluble A β and/or clear A β plaques post formation. Still, soluble A β peptides may similarly be protective *in*

vivo as an ameliorative response to free radical toxicity [Masters *et al.*, 1985, Nunomura *et al.*, 2010].

Inhibition of A β accumulation and aggregation—One therapy method currently under investigation seeks to prevent the toxicity associated with A β by inhibiting its accumulation *a priori*. In this vein, the modulation of enzymes responsible for the cleavage of A β PP to potentially detrimental A β peptides is one strategy of interest. The aspartyl proteases β - and γ -secretase work in sequence to cleave A β PP to A β ; consequently, drug treatment aims to inhibit the enzymes and thereby limit concentrations of extracellular A β [Marlatt *et al.*, 2005, Lundkvist *et al.*, 2007]. Numerous pharmacological agents, including NCT00594568, NCT00762411, GS1-136, and MK0752 [Neugroschl *et al.*, 2009], are under current study; most notably, the β secretase inhibitor Posiphen is in Phase I clinical trials [Sabbagh, 2009], and the γ secretase inhibitor LY450139 is in Phase III clinical trials [Wong *et al.*, 2004, Barten *et al.*, 2005, Lundkvist *et al.*, 2007]. Results of these trials are much anticipated and will further elucidate the future role of β - and γ -secretase inhibitors in AD treatment.

In addition to prevention of A β accumulation, the inhibition of A β aggregation is of much current interest. In this regard, nanoparticle metal chelators present an exciting future avenue to accomplish anti-aggregation of A β . Redox metals iron and copper are shown to be elevated in AD brain [Honda *et al.*, 2004, Smith *et al.*, 2009] and appear to induce A β oxidation and self-assembly [Bush *et al.*, 1994, Atwood *et al.*, 2000, Jobling *et al.*, 2001, Exley, 2006]. Consequently, metal chelators attempt to obstruct the interaction of A β and redox metals to prevent aggregation in AD vulnerable neurons. Metal chelators such as ethylenediaminetetracetic acid (EDTA), desferrioxamine, and iodochlorohydroxyquin (clioquinol) [Crapper Mclachlan *et al.*, 1991, Regland *et al.*, 2001, Ritchie *et al.*, 2003] can prevent the detrimental interaction between redox metals and A β [Schubert *et al.*, 1995, Opazo *et al.*, 2002, Liu *et al.*, 2006]. Unfortunately however, they cannot cross the BBB. To address this, current studies suggest utilizing nanoparticle conjugation to efficiently deliver metal chelators across the BBB [Liu *et al.*, 2009]. Specifically, the Nano-N2PY conjugate has been shown to thwart A β -induced toxicity in neuronal cell lines without impacting cell proliferation and growth [Liu *et al.*, 2009]. Nanoparticle-conjugated metal chelators remain in early-stage preparation as the pharmacological agents have yet to be administered in an animal model, but present a promising future treatment nonetheless.

Further along in drug development, the neurohormone melatonin also shows promise as an inhibitor of A β aggregation. In detail, long-term administration of melatonin to A β overexpressing Tg mice significantly attenuated senile plaque deposition in the entorhinal cortex and hippocampus [Olcese *et al.*, 2009]. This effect was most likely due to melatonin's ability to prevent fibrillization of A β [Fraser *et al.*, 1991, Pappolla *et al.*, 1998, Poeggeler *et al.*, 2001], though melatonin also had the beneficial effects of reducing oxidative stress and pro-inflammatory cytokines [Olcese *et al.*, 2009]. The clinical safety of melatonin administration in humans is confirmed, so all that remains is the completion of a large-scale Phase III clinical trial of melatonin in AD patients which will most likely take place in the near future.

Finally, in addition to nanoparticle-conjugated metal chelators and melatonin, the cyclohexanehexol stereoisomer, scyllo-inositol (ELND005) is under current study for A β aggregation prevention [Sabbagh, 2009]. Specifically, the molecule showed a reduction of insoluble A β and reversed cognitive decline in A β overexpressing Tg mice [Rogers *et al.*, 1993]. With Phase I trials complete, ELND005 will produce much anticipated results from a Phase II clinical trial in mid-2010 [Scharf *et al.*, 1999].

Degradation of A β —Once A β begins to accumulate and aggregate, a third treatment strategy may prove to be efficacious: degradation of insoluble extracellular A β . Immunotherapy directed against A β oligomers is highly touted as the solution to A β deposition despite a high risk of adverse effects and questionable patient outcomes [Perry *et al.*, 2000, Smith *et al.*, 2002]. Active immunotherapy involves introducing an A β antigen into the host system to induce the production of antibodies which bind A β and target the insoluble peptide oligomers for degradation and clearance. The initial trial of active immunotherapy with compound AN1792, an aggregated amyloid peptide, was prematurely terminated due to the development of meningoencephalitis in a significant percentage of enrolled patients (6%). This phenomenon was attributed to aberrant T-cell activation [Marlatt *et al.*, 2005]. Hence, several new A β antigens are in development which produce lowered T-cell activation, including ACC-001 and CAD106, both of which are in current Phase II trials.

As an alternative to active immunization, passive immunotherapy involves the injection of a preformulated anti-A β antibody, thus necessitating much less involvement of the patients own immune system. In this category, the humanized anti-A β monoclonal antibody Bapineuzumab (AAB-001) is in Phase III clinical trials [NCT00667810] and unfortunately shows a paucity of positive results. Specifically, patients treated with Bapineuzumab show no temporal improvements in cognition (ADAS-cog), excluding post hoc analyses [NCT00676143, NCT00575055, NCT00574132]. Besides Bapineuzumab, several other passive immunotherapeutics are in various phases of clinical development including Phase II immunoglobulin and PF-04360365, and Phase III solanezumad (LY2062430) [Relkin *et al.*, 2009] [NCT00329082, NCT00749216, NCT00905372, NCT00904683, NCT00722046]. As noted previously, evidence suggests A β is actually an antioxidant elaborated by neurons as a neuroprotective agent against primary cellular insults involved in AD pathogenesis; therefore, as we have long contended, amyloid degradation strategies will likely continue to be disappointed because of a fundamentally flawed paradigm [Perry *et al.*, 2000, Smith *et al.*, 2002].

SYMPTOMATIC APPROACHES

Since preventative and disease-modifying treatments are presently unproven, additional symptomatic treatments besides the ChEIs mentioned are worth considering as an attempt to decrease the burden on those already afflicted with AD and improve functional outcome with symptomatic AD. Such approaches are scarce, although one potential avenue is antidepressant therapy.

Antidepressants

Approximately 35% of AD patients present with the crippling symptom of depression at some point in the disease course [Arbus *et al.*, 2010]. Depression is believed to appear in AD due to an insufficiency of the neurotransmitters serotonin, norepinephrine, and dopamine resulting from cortical atrophy. Consequently, the use of selective serotonin reuptake inhibitors (SSRIs) in AD has been widely studied. Though there are mixed results with particular drugs within the class [Rosenberg *et al.*, 2010], as a whole, SSRIs seem to improve symptoms of depression in AD patients and significantly enhance quality of life [Siddique *et al.*, 2009]. In addition, in patients treated with ChEIs, the addition of SSRIs to the treatment regimen may actually protect against cognitive decline [Tan *et al.*, 1991]. Though antidepressants do not appear to target the disease process of AD [Hampel *et al.*, 2009], their use is still extremely valuable in symptomatic relief. Moreover, antidepressant therapy is, to date, the only therapeutic intervention that has shown significant improvement in subjects with mild cognitive impairment [Doody *et al.*, 2009].

CONCLUSIONS

Although AD pharmaceuticals on the market today, including ChEIs and NMDA antagonists, fail to alter disease progression, the development of new agents utilizing novel treatment strategies is certain. Numerous preventative treatments, specifically those aiming to avert oxidative stress (i.e., antioxidants) and neuroinflammation, are in the clinical testing phases and offer some hope for upstream therapy that may blunt the neurodegenerative process. Similarly, pharmaceuticals that stabilize mitochondrial function, ablate LH production, and obstruct the detrimental effects of hyperphosphorylated tau and A β , may play a role either alone, or, more likely, in combination, with other approaches. Since, to date, the neurodegenerative process has been unaffected by the spectrum of approaches, a broadening of that spectrum, rather than a narrowing of the focus on failed constructs, is the logical approach.

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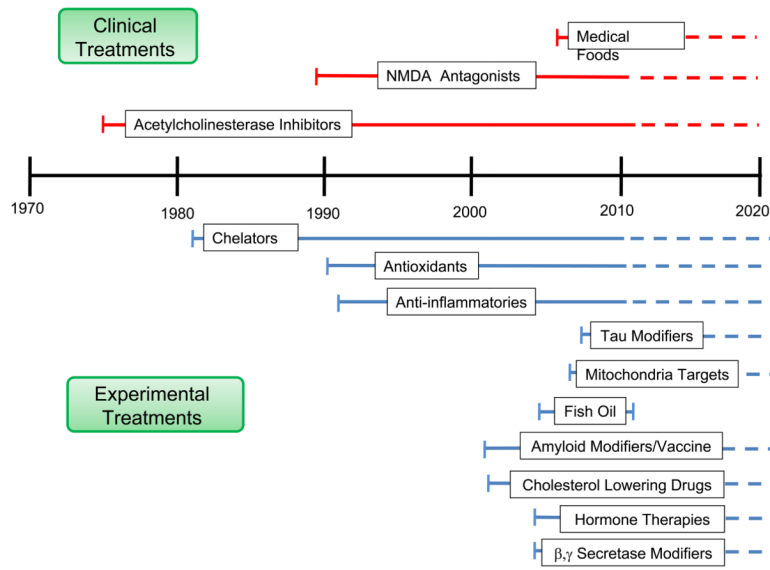


Figure 1. Timeline of the emergence of various experimental and clinical AD therapies.