Current therapeutic strategy in Alzheimer’s disease

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Abstract. – Alzheimer’s disease (AD) is a chronic, progressive, neurodegenerative disorder that places a substantial burden on patients, their families, and society. Alzheimer’s disease (AD) is the sixth leading cause of all deaths in the United States, and the fifth leading cause of death in Americans aged 65 and older. During the past years, several agents have been approved that enhance cognition and global function of AD patients, and recent advances in understanding AD pathogenesis has led to the development of numerous compounds that might modify the disease process. A wide array of antiamyloid and neuroprotective therapeutic approaches are under investigation on the basis of the hypothesis that amyloid beta (Aβ) protein plays a pivotal role in disease onset and progression and that secondary consequences of Aβ generation and deposition, including tau hyperphosphorylation and neurofibrillary tangle formation, oxidation, inflammation, and excitotoxicity, contribute to the disease process. Interventions in these processes with agents that reduce amyloid production, limit aggregation, or increase removal or vaccination and immunization might block the cascade of events comprising AD pathogenesis. Reducing tau hyperphosphorylation, limiting oxidation and excitotoxicity, and controlling inflammation might be beneficial disease-modifying strategies. Potentially neuroprotective and restorative treatments such as neurotrophins, neurotrophic factor enhancers, and stem cell-related approaches are also under investigation.

Key Words: Alzheimer’s disease, Inflammation, Hyperphosphorylation, Neuroprotection.

Introduction

Nearly a century has passed since Alois Alzheimer provided his meticulous description of the impaired cognitive performance and neuropathological analysis of his patient “Auguste”. His observations still guide expanding efforts in both clinical medicine and basic research to uncover the pathogenesis of the brain degeneration and, ultimately, develop therapeutic interventions that prevent or slow progression of Alzheimer’s disease. Alzheimer’s disease (AD) is a challenging neurodegenerative disorder in elderly causing dementia characterized clinically by progressive memory loss and other cognitive impairments. The research in AD is expanding exponentially and currently aiming at clinical, cellular molecular, genetics and other therapeutic research approaches. AD is not simply short memory loss but also results in other cognitive symptoms such as memory loss, disorientation, confusion, problems with reasoning and thinking and behavioral symptoms such as agitation, anxiety, delusions, depression, hallucinations, insomnia and wandering. Neuropathologically, presence of extra neuronal plaques and intraneuronal neurofibrillary tangles two characteristic lesions in post-mortem brain, where as clinically generalized progressive dementia are the major hallmarks of AD. Increased neuronal iron in an active redox state, increased nitric oxide (NO) synthesis in microglia and abnormalities in mitochondrial genome are assumed as additional contributory sources. Also lipid peroxidation (LPO) a hallmark of oxidative tissue injury has been found to be elevated in the AD brain. An understanding of these underlying mechanisms will certainly form the basis for devising better strategies for diagnosis, prevention and treatment. During the last couple of years, much has been learned about factors that may contribute to the onset of AD.

Antiamyloid Approaches

Proteolytic processing enzymatically of transmembrane amyloid precursor protein (APP)
forms Aβ peptides. According to amyloid hypothesis these Aβ peptides initiate the process leading to neuronal dysfunction and death in patient suffering from AD. No anti-amyloid treatment options are currently available, but several are under active investigation.

**Vaccination and Immunization Therapies**

Studies so far have shown that passive transfer of Aβ monoclonal antibodies from vaccinated mice to AD model mice reduced cerebral amyloidosis. Such effects are suggested to be mediated at least partially by reactive microglia that became activated to engulf antibody decorated Aβ via Fc receptor mediated phagocytosis. Passive transfer of Aβ-antibodies discouraged the active immunization which is potentially unsafe and damages autoaggressive CD4+T cells response to show aseptic meningoencephalitis in a small percentage of patients. So, passive immunization has emerged as alternative to active immunization. The first efficacy analysis conducted in a small subset of AN1792-treated patients showed antibodies generated against Aβ and significantly slower rates of decline in cognitive function and activities of daily living. Recent studies of using combinations in 3X TG AD mouse model reported amelioration of behavioral deficits clearance of cerebral amyloidosis and reduction of soluble hyperphosphorylated tau proteins. AN 1792 may have provoked brain inflammation in a small subset of treated individuals owing to the use of pro-inflammatory Th-1 adjuvant (QS-21).

However, Aβ vaccine with a full length 1-40 administered by a different route (intranasal route) produced significant Aβ antibodies titres and have effectively reduced cerebral Aβ plaque levels in the PDAAP mouse model. The antibodies, thus, produced were largely of IgG1 and IgG2b isotypes widely recognized as the B- cells epitopes. Studies in which transcutaneous Aβ vaccination with a full length of Aβ along with cholera-toxin to PSAPP mouse model where brain to blood efflux was noted and reduction of cerebral Aβ levels by 50% have been reported. Furthermore, no induction of micro hemorrhage and nil aseptic inflammation which were earlier reported after passive Aβ immunization in AD mice were observed. Several trials with passive immunization or vaccination with selective Aβ monoclonal antibodies are underway. Immunoglobulin G (IgG) contains anti-Aβ antibodies, and passive immunization of AD patients with IgG has been tested in a preliminary clinical trial. This novel approach in current theme of research and further detailed studies of this approach are planned.

**β-Secretase Inhibitors**

β-Secretase, a member of the peptin family, is a membrane-anchored aspartyl protease. Aβ is generated from APP by β and γ-secretase-mediated cleavage. The therapeutic potential of β-secretase inhibition, with limited mechanism-based toxicity, has been suggested by studies conducted in β-site APP cleaving enzyme 1 (BACE-1) knockout mice, which were shown to produce much less Aβ from APP. Injection of the β-secretase inhibitor KMI-429 into the hippocampus of APP transgenic mice significantly reduced Aβ production in vivo. Development of β-secretase inhibitors is challenging because of constraints of the active site; however, several small molecule agents are under active investigation.

**γ-Secretase Inhibitors**

Reductions in Aβ levels in the brain, cerebrospinal fluid (CSF), and plasma have been reported in rodents treated with the γ-secretase inhibitors DAPT. Acute treatment with DAPT at a dose that reduced Aβ concentrations in the brain attenuated cognitive impairment in a transgenic mouse model of AD, with no effect on performance in controls. This study suggested that cognitive impairments in AD might be associated with Aβ, potentially in advance of plaque formation, and might be reversible with acute pharmacologic treatment. In a randomized, controlled clinical trial conducted in 70 patients with mild to moderate AD, plasma Aβ 1-40 decreased by 38% with administration of LY450139 di-hydrate for 6 weeks, whereas CSF Aβ1-40 levels showed no significant change. Treatment with the γ-secretase inhibitor was well-tolerated. Further investigation is needed to determine whether higher doses will yield more beneficial changes in Aβ concentrations without an increase in toxicity. Safety in γ-secretase inhibitor trials is closely scrutinized because agents with limited selectivity might affect proteins beyond Aβ-related γ-secretase, such as Notch, and might have deleterious effects on the gastrointestinal tract, thymus, and spleen.

**γ-Secretase Modulators**

Chronic CHF5074 treatment reduced brain β-amyloid burden, associated microglia inflammation and attenuated spatial memory deficit in
Overall benefit after 12 months of treatment in patients with mild or moderate AD showed no improvement compared with placebo. Negative findings from recent controlled clinical trials of individual NSAIDs suggest that protection against AD is not a benefit provided by the entire class. Tarenflurbil (MPC-7869) modulates γ-secretase to produce less of the toxic form of Aβ (Aβ42) and more of the nontoxic shorter length peptide. Tarenflurbil reduces Aβ production by human cells and reduces plaque burdens in transgenic mouse models of AD.

An ongoing phase III study is further testing the antifibrilization agents. Current therapeutic strategy in Alzheimer’s disease.
terol might affect Aβ deposition or clearance. Interestingly, by blocking the conversion of free cholesterol to cholesterol esters results in similar effects on Aβ production in cell culture41,42. This process is carried out by acyl-coenzyme A: cholesterol acyltransferase (ACAT) as part of the regulation of cholesterol homeostasis. Pharmacological inhibition or genetic mutation of ACAT results in a reduction of total Aβ as well as Aβ42, indicating that the effects of cholesterol on APP processing might be mediated through cholesterol esters, although a role for a more direct effect of free cholesterol cannot be ruled out. A substantially reduced risk of AD has been reported in some (but not all) observational studies of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) used for the treatment of dyslipidemias43,44. The effect of statins on AD might not be mediated by their cholesterol-lowering properties. Rather, they might decrease Aβ by increasing processing of APP through the γ-secretase pathway45,46. In a recent randomized, double-blind, placebo-controlled pilot study in 63 individuals with normal cholesterol levels and mild to moderate AD, atorvastatin provided some clinical benefit after treatment periods of 6 months and 1 year47. However, several trials found no association with statin use and subsequent AD onset or cognitive decline48,49. Underscoring the need for further research with careful attention to study design and methodology. The U.S. National Institute on Aging (NIA) is sponsoring the Cholesterol Lowering Agent to Slow Progression (CLASP) of AD study to investigate the safety and effectiveness of simvastatin in slowing progression in patients with mild to moderate AD. Industry-sponsored, large phase III studies are ongoing as well. Treatment with rosiglitazone exhibited better cognitive performance on selected instruments after 4 and 6 months than patients receiving placebo51. AD subjects without an APOE e4 allele showed significant improvement with rosiglitazone compared with those with E4. No change from baseline plasma Aβ levels was observed with rosiglitazone treatment at 6 months, but decreases were seen with placebo, suggesting a beneficial impact on disease progression. A second study found a similar response profile limited to those without the E4 genotype, Pioglitazone, another PPAR-γ agonist, is also in clinical trials for mild-moderate AD54,55. Insulin itself might improve memory in AD. Craft56 demonstrated that intranasal insulin resulted in improvement in delayed recall in AD and MCI subjects.

**Metal-Protein Attenuating Compounds**

Aβ and APP interact with the biometals zinc, copper, and iron, indicating these metals play a role in Aβ aggregation and cytotoxicity57. Metal-protein attenuating agents such as clioquinol were tested to determine their effects on Aβ activity in animal and human studies. A study of APP transgenic mice treated with clioquinol showed a 49% decrease in Aβ brain deposition after 9 weeks, without systemic toxicity58. Clioquinol was associated with subacute myelo-optic neuropathy when administered as a systemic antibiotic in Japan in the 1950s to 1970s; studies of this drug were closely monitored for potential toxic effects. A pilot phase II clinical trial in 36 patients with moderately severe AD suggested that clioquinol might inhibit Aβ aggregation and reduce Aβ-related oxidative injury59. However, the statistically significant effects in this trial were observed only in the more severely affected subgroup of patients and were not maintained by the 36 week end point. Other metal chelators are being designed and tested in preclinical studies and clinical trials. A lipophilic metal chelator, molecule-XH1, with amyloid-binding and metalchelating moieties, reduced APP protein expression in human cells and attenuated brain Aβ amyloid pathology in APP transgenic mice60. The lipophilic metal chelator
DP-109 markedly reduced amyloid plaque burden in brains in APP transgenic mice and epigallocatechin-3-gallate, the main polyphenol constituent of green tea, which has metal-chelating and radical-scavenging properties, produced significant reductions in iron-regulated APP and Aβ peptide in cell cultures.

**M1 Muscarinic Agonists**

The M1 subtype of muscarinic acetylcholine receptors potentially plays a role in AD via several mechanisms, including effects on Aβ peptide, tau hyperphosphorylation, and cholinergic function. The M1 muscarinic agonist AF267B increased non-amyloidogenic APP processing in vitro and decreased brain Aβ levels in vitro and in vivo. In a recently developed Alzheimer’s mouse model characterized by both plaques and tangles, AF267B administration attenuated Aβ and tau pathologies in the hippocampus and cortex and improved some cognitive deficits. Past studies with the M1 agonist xanomeline demonstrated limited cognitive and behavioral effects in AD patients.

**Receptor for Advanced Glycation end Products-Related Mechanisms**

Several molecules have been identified that affect brain Aβ through mechanisms not included in the previously described classes. The receptor for advanced glycation end products (RAGE) resides in cells of the blood vessel walls and transports Aβ across the blood-brain barrier. Inhibition of the RAGE-ligand interaction reduces Aβ accumulation in the brains of transgenic mice. RAGE is a target for drug development.

**Peripheral Sink Approaches**

Gelsolin (GMI) has high affinity for peripheral Aβ, and administration of this agent results in binding of serum Aβ with creation of a “sink” pulling Aβ from brain to blood. This approach might lead to reduced brain amyloidosis in humans. Some vaccination strategies are also achieved through “sink” mechanisms. The Nogo-66 receptor (NgR) is a receptor for myelin inhibitor proteins and participates in limiting brain injury related axonal growth. There is an inverse correlation between Aβ levels and NgR levels within the brain. Administration of peripheral NgR reduces Aβ in the transgenic mouse brain, increases serum Aβ, and improves spatial memory. Such approaches might be of value in humans with AD, and drug development targeting this mechanism is underway.

**Neuroprotective approaches**

Aβ appears to exert some of its neurotoxic effects through numerous secondary pathways, including tau hyperphosphorylation and neurofibrillary tangle formation, oxidation, inflammation, demyelination, and excitotoxicity. These processes are potential targets for neuroprotective therapies.

| Table I. Drugs under clinical trial for the treatment of Alzheimer’s disease. |
|-----------------|---|-----------------|---|-----------------|
| Bapineuzumab-AAB001 | Phase III | Binds and removes Aβ-peptide |
| CAD 106 | I/IIa/IIb | Immunotherapy |
| AC1204 | Phase II/III | Targets glucose hypo metabolism by providing ketone bodies as alternative source |
| Acc-001 | I/IIa/IIb | Antibody vaccine |
| Affitope AD02/Mimotope Aβ (16) | I/IIa/IIb | Aβ (1-6) immunotherapy |
| α-Tochopherol | phase III | Destroys toxic free radicals |
| AZD 1446/TC-6683 | I/IIa/IIb | Nicotinic (nAChR) receptor activator |
| BMS-708163 | γ-secretases inhibitor |
| CERE-110/Nerve Growth Factor Gene Therapy | I/IIa/IIb | May reduce cholinergic cell loss in AD |
| Dimebon | Phase III | NMDA Inhibitor |
| DHA/Omega 3 fatty acid | Phase III | Modulation of presenilin |
| ELND005 | Phase II/III | Prevent Aβ-oligomeric formation |
| I.V. Immunoglobulin/IvIg | Phase III | Reduces Aβ and improves cognition |
| MABT5102A | Phase I | Binds and remove Aβ that accumulates in brain |
| Nicotinamide | I/IIa/IIb | Inhibitor of sirtuins |
| PBT2 | I/IIa/IIb | Inhibits oligomeric formation disaggregates plaques and neutralizes Aβ-toxicity |
| PF-04494700/TTP488 | I/IIa/IIb | RAGE-inhibitor (receptor for advanced glycation end products) |
Antioxidants

Oxidative injury is a common cause of cellular injury or death. Studies in a transgenic model of AD suggested that oxidative stress might be an important early event in the pathogenesis of disease. Conflicting results have been reported in longitudinal studies of the putative free-radical scavenger vitamin E in dementia-free elderly populations in Cache County, Utah, use of vitamin E and vitamin C supplements in combination was associated with reduced prevalence and incidence of AD. In research conducted by the Alzheimer Disease Cooperative Study, the effects of vitamin E, selegiline (a monoamine oxidase B [MAO-B] inhibitor), the two agents in combination and placebo were compared on time to death, time to nursing home placement, progression to severe dementia, or a defined severity of impairment of activities of daily living in participants with moderate AD. After adjusting for the severity of baseline cognitive impairment, there were significant delays in the onset of at least one of these four outcomes with vitamin E, selegiline, or combination therapy versus placebo after 2 years. In a recent double-blind study in patients with MCI, there were no significant differences between groups receiving vitamin E or placebo in the progression of AD. Several other antioxidants, including curcumin, are under investigation. Concerns about cardiovascular risk of vitamin E are emerging, and the risk/benefit ratio of high-dose vitamin E is being reexamined.

Astrocyte-Modulating Agents

The observation that Aβ plaques are surrounded by activated astrocytes that produce reactive oxygen and nitrogen species suggests that astrocyte activation might have a role in the pathogenesis of AD. In a rodent ischemia model, arundic acid (ONO-2506) decreased infarct size and improved neurologic outcome. The astrocyte-modulating agent protected dopaminergic neurons against neurotoxicity in a mouse model of Parkinson’s disease and prevented motor abnormalities by modulating astrocytic activation. The astrocyte-modulating compound ONO-2506 is undergoing assessment in a phase II clinical trial of patients with mild to moderate AD.

Homocysteine-Lowering Strategies

Concentrations of the sulfur-containing amino acid homocysteine, previously associated with cardiovascular risk, are reported to be higher in individuals with AD than in age-matched controls. Among dementia-free elderly individuals participating in the Framingham study, development of AD was greater in participants with elevated homocysteine concentrations than those without elevations. Evidence from APP transgenic mice suggested that increased homocysteine might hinder DNA repair in neurons, rendering them vulnerable to Aβ-induced damage and a recent study in mice found that increased homocysteine levels might exert toxic effects on brain micro vessels and disrupt the blood-brain barrier. A federally sponsored clinical trial of homocysteine lowering vitamin combinations is now in progress.

Anti-Inflammatory Agents

Certain Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been shown to modulate γ-secretase activity in mammalian cells and in mice. NSAIDs alter the specificity of γ-secretase, decreasing the production of Aβ42 and increasing the production of a shorter form of Aβ that terminates at residue 38. So, although the mechanism by which these compounds affect γ-secretase is unclear — for example, direct versus indirect effects their ability to reduce Aβ42 selectively and the fact that they are already known to be safe for human use has spurred plans for their use in clinical trials for the prevention and/or treatment of AD. Processing of APP by α-secretase does not lead to Aβ production. However, stimulation of α-secretase-mediated processing of APP reduces Aβ formation, presumably by shunting more APP down this alternative pathway. Such stimulation can be accomplished by the activation of protein kinase C (PKC); for example, by treatment with phorbol esters. More practically, PKC can be activated by muscarinic M1- and M3-receptor agonists and such agents are considered reasonable candidates for AD therapy. Potential problems with this strategy might be undesirable side effects as a consequence of the chronic activation of muscarinic receptors. The first demonstration that muscarinic agents can modulate APP processing. Although microscopic evidence of inflammation has been observed in the brains of patients with AD, a series of controlled clinical trials demonstrated no significant benefit with prednisone, diclofenac, rofecoxib, nimesulide, or naproxen in slowing the rate of decline in AD. In a recent double-blind study of patients with MCI, rofecoxib did not significantly delay the diagnosis.
of AD or improve cognitive or global function. A disease-modifying effect of anti-inflammatory agents is plausible but not supported by currently available clinical trial data. Potential benefits of these agents must be weighed against risk of side effects including gastrointestinal bleeding.

NMDA-Receptor Antagonists
Cognitive decline in patients with AD has been linked with neuronal damage from excite toxicity caused by persistent over activation of NMDA receptors by glutamate. Both Aβ and over expression of tau proteins, appear to be triggers for the excessive activation of NMDA (N-methyl-D-aspartate) receptors and the resulting excite toxic pathway that leads to cell death.

The NMDA receptor antagonist memantine, approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe AD, might reduce glutaminergic excitotoxicity and provide symptomatic improvement by affecting neuronal function in the hippocampus. A randomized, double-blind, placebo controlled phase III study conducted in the U.S. in patients with moderate to severe AD showed significant improvement with memantine (20 mg/day) versus placebo in activities of daily living and neuropsychological outcomes. No clinically relevant differences were observed in the safety profiles of memantine and placebo. In a second U.S. controlled clinical trial, memantine administered in combination with the cholinesterase inhibitor donepezil in patients with moderate to severe AD was also associated with significantly increased cognitive function, decreased decline in activities of daily living, and decreased incidence of new behavioral symptoms when compared with placebo. Other NMDA receptors, including neramexane (MRZ 2/579), have demonstrated neuroprotective potential in preclinical investigations and are proceeding to clinical development. In a double-blind, randomized, placebo-controlled phase II clinical trial conducted in 198 patients with moderate to severe AD, patients receiving neramexane therapy for 24 weeks had significantly greater improvement in activities of daily living compared with patients receiving placebo. However, no significant difference was demonstrated in measures of cognitive function.

AMPA-Receptor Modulators
Glutamate activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors is believed to mediate most fast synaptic neurotransmission in the brain. An investigation in mice demonstrated glutamate AMPA receptor involvement in the regulation of sensorimotor, affective, and cognitive functions. Positive AMPA receptor modulators might have utility in a broad spectrum of neurologic pathologies, with tests in preclinical models suggesting potential neuroprotective effects and enhanced cognitive performance. In a double-blind, placebo-controlled, phase II trial, the efficacy and safety of the AMPA receptor modulator CX516 were evaluated in 175 patients with MCI. The CX516 treatment group did not demonstrate significant improvement in delayed recall of a 15-item list compared with the placebo group after 4 weeks of treatment. A subset analysis showed that the patients with the worst baseline memory impairment exhibited improvement in the delayed recall test with CX516 versus placebo. A significant difference in patient withdrawals was observed between the CX516 and placebo groups, primarily related to gastrointestinal side effects, but no treatment-related serious adverse events were reported in either group. Further development of this class of compounds is warranted.

Tau-related Therapies
Phosphorylation of tau proteins, critical for the production of intracellular neurofibrillary tangles, is dependent on Intracellular kinases such as glycogen synthase kinase 3 (GSK3) Lithium has been shown to reduce hyperphosphorylation of tau proteins by inhibiting GSK3 in cell culture and in transgenic mice. Through its inhibitory actions on GSK3, lithium also blocks the accumulation of Aβ peptides in the brains of mice that overproduce APP. This agent could prove beneficial by reducing the formation of both neurofibrillary tangles and amyloid plaques, but its toxicity in older adults might limit its use. A second mood stabilizer, valproic acid, has been reported to inhibit GSK3, and there is an ongoing NIA sponsored trial of valproic acid in mild to moderate AD. Tau hyper phosphorylation and formation of intracellular neurofibrillary tangles might be the principal cell death pathway in AD. Inhibitors of this process might be necessary to complement effects of anti-amyloid therapies. For example, a recent report demonstrated that transgenic mice with cerebral amyloidosis demonstrate a reduction in behavioral deficits when tau levels are lowered, without a concomitant lowering of the cerebral amyloid bur-
Drug discovery efforts are underway to identify viable therapeutic tau-modulating candidates.

**Caspase Inhibitors**

Caspase enzymes might represent an important link between amyloid plaques and neurofibrillary tangles in AD as well as being critical to cell death pathways. Neurons treated with Aβ peptide activate caspases, which trigger cleavage of tau and produce truncated forms of the proteins that rapidly and extensively assemble into abnormal filaments characteristic of the tangles found in AD\(^{118}\). Caspase activation is also required for apoptosis in forebrain neurons\(^{119}\) and is increased in the brains of patients with AD\(^{120,121}\). Exposure of cortical cell cultures to a caspase-3 inhibitor blocked caspase-induced cleavage of tau\(^{122}\). In addition, caspase inhibitors have prevented neuronal damage or loss in animal models of head injury and stroke suggesting this approach might have utility in the treatment of AD\(^{123,124}\).

**Nicotine Acetylcholine Receptor Agonists**

There are significant losses of some nicotine acetylcholine receptor (nAChR) subtypes on neurons in the hippocampus and temporal cortex of patients with AD, concurrent with significant increases in the number of astrocytes and astrocytes expressing the 7 nAChR subtype. The increased expression of 7 nAChRs on astrocytes is positively correlated with the number of neuritic plaques, suggesting a potentially important role for this receptor subtype in disease pathogenesis. Nicotine treatment of transgenic mice that over express Aβ with nicotine results in a reduction in cortical Aβ levels with short-term administration and a reduction in amyloid plaque formation and 7 nAChR expression with long-term administration\(^{125}\). In animal models, nicotine produces enhanced performance on working memory tasks\(^{126}\). Galantamine, a cholinesterase inhibitor with nicotinic modulating properties, reduces APP metabolism in an animal model of AD\(^{127}\). The 4-2 nAChR partial agonist ispronicline (TC-1734) has demonstrated memory-enhancing properties in rat and mouse models, neuroprotective effects in studies in cultures and hippocampal slices, and a positive safety/tolerability profile in phase I clinical studies\(^{128}\). Phase II studies showed some improvement in cognitive function in ispronicline-treated patients with age-associated memory impairment and MCI; additional phase II studies in AD patients are underway.

**Cholinesterase Inhibitors**

Cholinesterase inhibitors augment cholinergic function in AD at the postsynaptic cholinergic neuron. This pharmaceutical class reduces acetylcholinesterase-induced destruction of acetylcholine in the synaptic cleft, increases the intrasynaptic residence time of acetylcholine, and facilitates interaction between acetylcholine and the postsynaptic cholinergic receptor. Cholinesterase inhibitors are used primarily as long-term symptomatic treatment for AD. Evidence derived from clinical trials\(^{129}\), imaging\(^{130}\) and basic science studies suggest that cholinesterase inhibitors might reduce APP processing and provide some degree of neuroprotection\(^{131-135}\).

Most long-term clinical observations indicate the principal effect of cholinesterase inhibitors is symptomatic treatment with limited disease modifying activity\(^{136}\).

**Neuroprotective and Neurorestorative Approaches**

Nerve growth factor (NGF) is a member of the neurotrophin family of polypeptides. Other members of this protein family exhibit similarities in structure and function and include neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and brain-derived neurotrophic factor (BDNF). Each of these growth factors plays an important role in normal neural development and maintenance of the mature central and peripheral nervous systems, including mediation of neuronal proliferation, differentiation, and neuronal survival\(^{137}\). NGF, like other neurotrophins, promotes cell survival by signaling through specific tyrosine kinase receptors, thereby engaging internal cellular machinery to effectively block apoptosis from occurring in either a developing or damaged neurons. Given their survival-promoting properties, neurotrophins are considered potential therapeutic agents for neurodegenerative disease\(^{138}\). Specifically for AD, evidence from studies in mice suggests that NGF might play a significant role in maintaining neuronal integrity, as well as survival in response to injury of the basal cholinergic forebrain neurons. A lack of endogenous NGF can lead to memory deficits, whereas NGF administration rescues neurons from injury-induced cell damage and leads to associated memory improvements\(^{139,140}\). Hence, NGF and NGF-related agents might have neurorestorative as well as neuroprotective properties. The impermeability
of the blood-brain barrier to exogenous NGF and other neurotrophins presents a significant challenge for evaluation of potential therapeutic benefits in AD. Strategies to circumvent this transport challenge are the surgical implantation of NGF-expressing cells (eg, gene therapy)\(^\text{141}\) or administration of agents that or potentiate the endogenous production of NGF and other neurotrophins\(^\text{142,143}\). The nonpeptidic agent xaliprodren (SR-57746), a neurotrophic factor enhancer (NTFE), demonstrates neurotrophic effects in several preclinical neurodegenerative \textit{in vivo} and \textit{in vitro} models\(^\text{144}\). Xaliprodren activates endogenous neurotrophin synthesis, including NGF and BDNF, in rat cortical astrocytes\(^\text{145}\). In a rat model of the forebrain cholinergic neuron and memory deficits of AD, xaliprodren reversed hippocampal choline acetyltransferase reduction (a measure of cellular activity and viability) and decreased behavioral disturbances\(^\text{146}\). Magnetic resonance imaging demonstrated the neuroprotective effects of xaliprodren in this model Ongoing, randomized, controlled, phase III trials are currently assessing effects of this agent on cognitive and global functions in patients with mild to moderate AD Cerebroylin (FPF 1070), a peptide mixture with neurotrophic activity, enhances synaptic regeneration, reduces Aβ deposition, and ameliorates performance deficits in APP transgenic mice\(^\text{147}\). Randomized, double-blind, placebo controlled studies show that cerebroylin infusions significantly improve activities of daily living and cognitive function\(^\text{148,149}\). Reported rates of adverse events are similar across treatment and placebo groups. Targeted delivery of human NGF by gene transfer prevents injury-induced degeneration of cholinergic neurons in adult monkeys\(^\text{150,151}\). In a recent phase 1 study, genetically modified, autologous fibroblasts producing human NGF were implanted into the forebrains of six patients with mild AD. After an average follow-up period of 22 months, no long-term postsurgical adverse events occurred, and the rate of cognitive decline appeared to be ameliorated. Clinical investigation of this approach is expected to continue.

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