Recent Therapeutic Approaches for Management of Alzheimer’s Disease

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Development of novel therapies for Alzheimer’s disease has now been given much attention, with an aim to search for more potent drugs for long term use through various approaches and hypothesis. Five distinct hypotheses/approaches for the therapies have been discussed in this review, namely, (1) cholinergic hypothesis, (2) hormone replacement approaches, (3) antiinflammatory approaches, (4) neurotrophic approaches and (5) an approach to inhibit formation of amyloid and neurofibrillary tangles. In the cholinergic hypothesis, acetylcholinesterase inhibitors have been more successful and potent compounds have been identified that include tacrine, physostigmine, donepezil and rivastigmine. Among these, tacrine and physostigmine have been associated with toxicity and bioavailability problems respectively and donepezil and rivastigmine have been launched in the market. Estrogen has shown efficacy in the treatment of Alzheimer’s disease giving rise to the hormone replacement approach. Few antiinflammatory drugs such as ibuprofen, naproxen and rofecoxib have shown promise in long term therapy against Alzheimer’s disease. Agents that stimulate neurotrophic effects such as citicoline, anapsole and AITS-C32 have shown progress in treatment of mental impairment and are at different stages of clinical trials. Few amino acid derivative, amine and urea analogs and hydorxy-hexamide have been shown to inhibit amyloid β synthesis or/and release.

The life span of human is increasing and with this expanded life span comes the risk of developing Alzheimer’s Disease (AD). The etiology of this disease dates long back to 1907, first recognized by Professor Alois Alzheimer in Germany in a 55-year old woman with dementia, senile plaques and neurofibrillary tangles by autopsy. Recent finding reveals that elderly patients have high risk of developing AD. Differences between early and late onset cases are reflected in the neurochemical pathology, which was found more severe in the young onset patient. However, it is now recognized that AD is a major cause of mental impairment (dementia) and loss of memory function. The prevalence rates of disease per 100 population is about 0.02 in the 50 to 59 year age group, 0.3 in the 60 to 69 year age group, 3.2 in the 70 to 79 year age group and 10.8 in the 80 to 89 year age group. The management of AD is too complex and frustrating because there is no specific treatment and the primary focus is on long-term amelioration of associated behavioral and neurological problems. In last few decades, different hypothesis and approaches were proposed for the treatment of AD, viz., the cholinergic hypothesis, hormone replacement approaches, antiinflammatory approaches, agents that stimulates neurotrophic effects, and inhibition of amyloid formation and neurofibrillary tangles. This review attempts to provide current therapeutic approaches for AD and provide a useful perspective for the future drug development.

THE CHOLINERGIC HYPOTHESIS

According to the cholinergic hypothesis, memory impairment in patients with senile dementia of AD results from a deficit of cholinergic function. It was found in the postmortem analysis of AD affected brains that the loss of

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cholinergic innervation of the hippocampus and cerebral cortex coupled with the loss of cholinergic neurons in the basal forebrain. Therefore, treatment for memory loss in AD has mainly been focused on cholinergic hypothesis. Three different approaches of enhancing cholinergic function include increase acetylcholine (ACh) levels using acetylcholinesterase (AChE) inhibitors or administration of ACh precursors or ACh releasing agents or inhibition of ACh degradation and directly stimulating cholinergic receptors using cholinomimetics.

**Acetylcholinesterase Inhibitors:**

The enhancement of the central cholinergic function has been regarded as one of the most promising approaches for the treatment of AD by means of AChE inhibitors. Recent studies have shown that AChE inhibitors interact with both peripheral and active site of enzyme. In addition to AChE inhibition, it also acts as potential inhibitor for formation of amyloid β (Aβ)\(^{11-13}\). Many research groups have reported over the last decade on compounds that inhibit AChE as approaches to treat AD.

Tacrine (THA) (1) was found to be a potent acetylcholinesterase inhibitor\(^{14-17}\) in 1953 and subsequently its derivatives such as velnacrine (2) and surcinacine (3) have been reported as AChE inhibitors for the treatment of the AD\(^{18}\). Unfortunately, tacrine has shown side effects such as hepato toxicity and gastrointestinal upset. Recently, THA-based compounds have been reported, and these compounds showed in vivo AChE inhibition in rat cortex or whole brain\(^{18-20}\). In addition to this, many compounds have been reported as AChE inhibitors such as aza analogues of tacrine, New tacrine-huperzine A hybrids (4)\(^{21}\).

Later, a number of compounds have been studied for this purposes\(^{22-23}\) viz., 4-aminopyridine, 4-aminoquinoline, and tetrahydro acridine and 9-(N-n-butyl amino) 1,2,3,4-tetra acridine. The results reveal that 4-aminopyridine and 4-aminoquinoline have very weak AChE activity although their basicities were almost equal to that of tacrine. The N-butyl derivatives was not particularly active, with the butyl chain hindering the interaction of the compound with the enzyme, but tetra hydro acridine, a much weak base was found to be as active as tacrine.

Physostigmine (5) has been reported to have memory enhancing effect in AD\(^{24}\). Unfortunately, again, it has short half-life, variable bioavailability and narrow therapeutic index. Heptyl physostigmine a more lipophilic analogue is reported to be less toxic than physostigmine while retaining
its *in vitro* AChE inhibiting potency. 8-carba physostigmine has greater potency and reduced toxicity compared to physostigmine. Galanthamine (6) is a reversible inhibitor of cholinesterase and an allosteric modulator of nicotinic acetylcholine receptor. It is well tolerated during long-term treatment, and is under clinical evaluation for the treatment of AD.

The N-benzyl piperidine analogues such as 1-benzyl-4-[2-(N-benzyloxylamino)-ethyl] piperidine, 1-Benzyl 4-1-[2-(N-phthalimidoethyl)] piperidine, 1-Benzyl-[5,6-dimethoxy-1-indanone-2-y] methyl piperidine HCl (donepezil) (7) have been reported by Sugimoto et al. to possess the AChE inhibitory activity. 

Villalobos et al. has reported N-benzyl piperidine benzisoxazolones, containing benzoisoxazole ring, which was identified as a suitable bioisosteric replacement for the benzyl moiety present in the compounds reported by Sugimoto et al.

(-)-Huperine A (8) originally obtained from the Chinese herb, *Huperiza serrata*, is a reversible inhibitor of AChE, which is reported to have entered clinical trials for alleviation of AD. A more powerful compound namely, huprine has been reported as more potent AChE inhibitor, being a 40 fold more potent than donepezil and 180 fold potent than (-) huperine A.

Donepezil (7) and rivastigmine (9) have been marketed recently for the treatment of the cognitive symptoms of AD. Use of AChE inhibitors in combination with Vitamin E is generally considered for earlier stage of the disease. Vitamin E increases the brain catecholamine and reduces the oxidative damage to neurons thus the progress of AD.

In the recent past, a hexahydrochromeno [4,3-b] pyrrole derivative has been reported as AChE inhibitor activity. An amino pyridazinc analogue, minaprine (10) has been reported to have AChE inhibitory activity in homogenized rat striatum. An *in vivo* administration of minaprine (30 mg/kg) to rats significantly increase acetylcholine level in the hippocampus (38%) and striatum (60%) Further studies and optimization of minaprine led to the identification of 3-[2-(1-benzylpiperidin-4-yl) ethylamino] pyridazine and 3-[2-(1-benzylpiperidin-4-yl) ethylamino] methyl-6-phenyl pyridazine. This shows an IC₅₀ of 0.12 μm and 21 nm respectively, on purified AChE (electric eel), as a potent AChE inhibitor. The 3-[2-(1-benzylpiperidin-4-yl) ethylamino] pyridazine, representing a 5000 fold increase in potency compared to minaprine. Recently a study on a series of
[N-methyl-N-(3-alkylcarbamoylophenyl) methyl] aminoalkoxyaryl derivative, an azoxanthone derivative, reported as AChE inhibitors by Rampa et al., which are more potent than tacrine but less than donepezil\textsuperscript{45}, and showed AChE inhibitory activity in rat cortex.

**Cholinergic agents:**

The cholinomimetic effect of these compounds is based on increase in the amount of ACh precursor choline. Compounds that have such a cognition stimulating mechanism include exogenous choline, lecithin and phosphatidyl choline. Glatilin (11)\textsuperscript{46} and acetyl-L-carnitine (ALCAR) (12)\textsuperscript{47} have been reported for the treatment of AD from this class.

**Acetylcholine release modulators:**

Acetylcholine release modulator, linopirdine (DUP-996) (13)\textsuperscript{50} enhances the potassium evoked ACh release from the rat cortex, hippocampus and caudate nucleus in vitro. This is now in phase III clinical trial. Another mechanism of the stimulation of the ACh is realized via antagonists of H\textsubscript{3} histamine receptors (H\textsubscript{3}-HRs). H\textsubscript{3}-HRs, a subtype of HR is localized on presynaptic terminals of histaminergic and non-histaminergic neurons in the central and peripheral nervous system. Two drugs namely, clobenpropit and thioperamide have been reported for the treatment of AD. Clobenpropit (14) is H\textsubscript{3}-HR antagonist, whereas, thioperamide (15) is H\textsubscript{3}-HR agonist, which belong to 4-substituted imidazole derivatives\textsuperscript{51,52}.

A stimulation of ACh release via the increase of the presynaptic uptake of endogenous choline, formed due to the AChE catalyzed enzymatic degradation of ACh is considered to be an alternative to the receptor regulated ACh release. MKC-231 (16) has been launched for AD from this class. It is an activator of the high affinity choline uptake the essential component of ACh resynthesis\textsuperscript{53}.

**Muscarinic agonists:**

Cholinergic agonist acting directly on muscarinic receptor may improve the cholinergic dysfunction seen in AD. In AD, the basal forebrain muscarinic neurons that predominately express the pre synaptic M2 receptors have been found in atrophy. However, mainly the presynaptic M1 receptors are highly concentrated in the cortex and hippocampus and their density is reported to be unaltered in AD. A preferential involvement of the M1 receptors in memory has been proposed. This suggests that M1 selective agonist may be useful. Several non-selective muscarinic
agonists such as arecoline (17)\textsuperscript{54}, RS-86 (18)\textsuperscript{55}, oxetremorine (19)\textsuperscript{56} and pilocarpine (20)\textsuperscript{57} have been evaluated in AD patients with disappointing results.

**HORMONE REPLACEMENT APPROACHES**

Estrogen replacement therapy in postmenopausal women resulted in a 40-50% reduction in the risk of developing AD. 17\(\beta\)-estradiol protects neurons against oxidative damage induced by A\(\beta\) as well as other oxidants such as hydrogen peroxide and glutamate. Animal studies have shown that the administration of estrogen to estrogen deficient laboratory animal restores the number of neural synapses, causing A\(\beta\) to be more soluble\textsuperscript{58}. It also induces and increases the activity of choline acetyl transferase, the rate-limiting enzyme for acetylcholine synthesis in both the basal forebrain and target area of cholinergic neurons\textsuperscript{59}.

**ANTIINFLAMMATORY APPROACHES**

Prostaglandins are implicated in the pathology of the AD. Recently, it has been reported that non-steroidal antiinflammatory drugs (NSAIDs) alleviate inflammatory changes in the brain of patients with AD\textsuperscript{60}. Although NSAIDs would not be expected to modify the abnormal metabolism of A\(\beta\), they could reduce the response of microglia to the protein. The neural damage in AD may be due to the inflammatory reaction with consequent free radical and protease release than to the presence of amyloid per se. Thus, inhibition of inflammation may delay or even abort the loss of neurons consequent on amyloid deposition. In a recent report, ibuprofen (21) and naproxen (22) have been found to reduce the severity of AD though paracetamol does not show any benefit. Ibuprofen is currently in phase III trials\textsuperscript{61-62}. FDA has approved rofecoxib (23) in 1999, for treatment of osteoarthritis, acute pain and dysmenorrhea. It is under investigation now in phase III clinical trials in AD patients\textsuperscript{62}.

**AGENTS THAT STIMULATE NEUROTROPIC EFFECTS**

Compounds namely, propentofylline (24), citicoline (25), anapest and ALT-082 (26) that have a neuroprotective and cognition-stimulating activity via stimulation of neurotrophic function in CNS. The main effect of propentofylline is the inhibition of the adenosine re-uptake system. This results in the accumulation of adenosine in CNS and consequent activation of adenosine receptor A1 type and A2 type that block the excitatory aminoacids. Further development of propentofylline, however, was discontinued after phase IIIb clinical trial due to decrease in the level of radical oxygen species and cytokines, which
results from suppressed activation of microglia in degenerative processes\textsuperscript{64}.

Citicoline an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain acetylcholine was extensively used for treatment of neurodegenerative disorders associated with head trauma, stroke, etc. During the past few years, it was shown that citicoline may improve memory via its neurotrophic effect\textsuperscript{65-66}. An herbal agent, anapso which is extracted from Filices Polypodium leucotomos, has improved cognition function, circulation of the blood and brain bioelectric activity in patients with senile dementia. It is important that positive effects of Anapso are well pronounced in patients with moderate form of AD-type dementia\textsuperscript{67}.

AIT-082 acts at the site of heme oxygenase to generate carbon monoxide and by activation of guanylyl cyclase induces a cascade of biochemical reaction through the second messenger system leading to the production of mRNA neurotrophins, it is currently in phase-III clinical trials\textsuperscript{68}.

**INHIBITION OF AMYLOID FORMATION AND NEUROFIBRILLARY TANGLES**

The proteolysis of the membrane anchored amyloid precursor protein (APP) results in the generation of the Aβ peptide that is thought to be causal for the pathology and subsequent cognitive decline in AD\textsuperscript{59-70}. The amyloid approaches postulate that agents that decrease Aβ level in vivo would have promising therapeutic benefit in AD\textsuperscript{71-72}. Amino acid derivatives (27,28)\textsuperscript{73,74}, amine and urea analogs (29,30)\textsuperscript{75,76} and hydroxy-hexanamide derivative (31)\textsuperscript{77} have been shown to inhibit Aβ synthesis or/and release. Apolipoprotein E-4 is found in both senile plaques and neurofibrillary tangles. ApoE-4 interacts with, and precipitates Aβ protein. Oxygen mediated complex formation was implicated. This suggests that antioxidant may have therapeutic potential in AD.

Two specific proteases involved in the production of the Aβ peptide are the β and γ secretases, which liberate the carboxy terminus of the peptide, though not fully established but are thought to be unusual aspartyl proteases\textsuperscript{78}. Dovey et al. have recently disclosed compounds that inhibit γ secretase in cells and demonstrated the reduction of brain Aβ levels in PDAPP transgenic mice\textsuperscript{79}. A number of groups have published on the isolation and cloning of β secretases (BACE), the enzyme involved in the proteolytic formation of the amino
terminus of the Aβ peptide and shown it to be a membrane bound aspartyl protease. The cleavage of APP by BACE occurs on its luminal side and is considered to be the rate limiting step in the processing of APP to Aβ. BACE is thus an attractive therapeutic target for the design of inhibitors of Aβ production. More recently, β secretase substrate derived inhibitors (IC₅₀=0.03 µm) and BACE inhibitors containing hydroxyethylene units as dipeptide isosteres (IC₅₀=30 nM), have been reported as potent inhibitors of BACE for the treatment of AD.

Along with senile plaques, neurofibrially tangles are characteristic histopathological lesions of AD. A major component of neurofibrially tangles is tau, a family of microtubule associated proteins which are important for the maintenance of the neuronal cytoskeleton. Neurofibrially tangles associated tau is excessively phosphorylated which may result from neural calcium dysregulation. Before incorporation in neurofibrially tangles, the abnormal phosphorylation of tau may lead to microtubule destabilization and cytoskeleton disruption resulting in impaired neuronal function and survival. Glycogen synthesis kinase-3 (GSK-3) has been proposed as possible phosphorylation enzyme for tau. Much recent report indicated that GSK-3 inhibitors viz., 3-anilino-4-aryl maleimides, 6-aryl-pyrazolo [3,4-b] pyridines, 6-heteroarylp-pyrazolo [3,4-b] pyridines, 5-aryl-pyrazolo [3,4-b] pyridazines, 1-(4-aminofuran-3-yl)-5-dialkylaminomethyl-1H-[1,2,3] triazoles-4-carboxylic acid derivatives, pyrazolo pyrimidines derivatives and 3-(7-azaindol-4-yl)-5-arylmaleimides, have therapeutic potential for treating Alzheimer disease by protecting neuron from death induced by reduced PI-3 kinase pathway activity. Statin derivatives such as simvastatin (32), atorvastatin (33) have also showed promising anti- Alzheimer activity, which would be based on their ability to reduce a lipoprotein oxidation, decrease inflammation, generation of radical oxygen species (ROS) and reduce the cerebral Aβ level.

CONCLUSIONS

The development of better drug for the treatment of AD has now been one of the targets for scientists in the research institute and pharmaceutical industry. In the recent past, a number of drugs have been in the market for early stage treatment of AD. The major limiting factors in their use are their pharmacokinetic and toxicity problems. In addition, there is no clear evidence that the long-term use of a particular drug will alleviate the AD. However, perfect understanding of pathophysiology will be a turning point to develop the anti-Alzheimer's agents. Further studies are needed on pathophysiology of AD in order to develop better and safer compounds for long term use against the later stage AD.

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