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ALZHEIMERS: A REVIEW ON CURRENT TREATMENT STRATEGIES

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia affecting our population, thought to be responsible for 70% of dementia. Dementia can be defined as the significant loss of intellectual abilities such as memory capacity, severe enough to interfere with social or occupational functioning. The clinical hallmarks of Alzheimer's disease are a progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language. Alzheimer's disease is the largest unmet medical need in neurology. Current drugs improve symptoms, but do not have profound disease-modifying effects. However, in recent years, several approaches aimed at inhibiting disease progression have advanced to clinical trials. Among these, strategies targeting the production and clearance of the amyloid-β peptide a cardinal feature of Alzheimer's disease that is thought to be important in disease pathogenesis are the most advanced. This article discusses recent progress with each of these strategies, with a focus on anti-amyloid strategies, highlighting the lessons learned and the challenges that remain.

Key Words: Alzheimers, Amyloid, Blood Brain Barrier, Dementia.

INTRODUCTION

There are many hurdles preventing interventions from reaching the diseased brain. Systemic delivery of therapeutics to the central nervous system (CNS) is ineffective for most small molecules and nearly all large molecules [1]. The main impediment in most cases is the blood brain barrier (BBB). Necessary for protection against bacterial infections, the BBB prevents most foreign substances, including potential therapeutics, from entering the brain from capillaries. Meanwhile, the BBB permits the diffusion of small hydrophobic molecules, which is often insufficient for pharmacotherapeutic targeting of the diseased brain. As a result, large doses of therapeutics including small molecules or peptides are required to achieve therapeutic levels in the brain, increasing the risk for adverse systemic effects [2]. Although therapeutics can be directly targeted to the brain via intra cerebroventricular or intra parenchymal delivery, these invasive techniques are not without risk and can necessitate repeated surgical intervention.

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Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia affecting our population, thought to be responsible for 70% of dementia [3]. Dementia can be defined as the significant loss of intellectual abilities such as memory capacity, severe enough to interfere with social or occupational functioning. The clinical hallmarks of Alzheimer's disease are a progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language. The clinical diagnosis of probable Alzheimer disease is usually made on the basis of the history obtained, supported by findings on neurologic examination and blood work to exclude metabolic and vitamin deficiencies, for example. However, a definitive diagnosis can be made only at autopsy.

VARIOUS STAGES OF THE DISEASE [4]

STAGE-I (Pre-Dementia):-A mild cognitive symptom which occurs in the initial stage within 2 months and is observed by the following actions such as attentiveness, planning, abstract thinking and semantic memory.

STAGE-II (Early-Dementia):- This is a moderate cognitive symptom which occurs after 20 years period before diagnosis and is observed by the following conditions such as impairment of learning, memory, fine motor tasks, language problems, episodic memory and vocabulary problems.

STAGE-III (Moderate-Dementia):- This is advance stage of moderate cognitive symptom which occurs for a period of 1 to 5 years and is observed by the following conditions such as progressive deterioration, increase in vocabulary problems, worsening of memory problems, wandering, sundowning, anognosia and urinary incontinence.

STAGE-IV (Advanced-Dementia):- This is a complete stage for a period above 10 years and is completely dependence on care givers. It is the mature stage of the disease which is observed by the following conditions such as bed ridden, unable to eat and g.i.t. internal problems (ulcer formation and pneumonia).

PATHOPHYSIOLOGY

Pathological changes in the Alzheimer's disease brain include cerebral amyloid plaques [5] inflammation and neurofibrillary tangles [6]. It is believed by many that these neuropathological changes are responsible for most of the condition [7] although other molecular changes occur and likely play an important pathophysiological role. There is increasing consensus that the production and accumulation of beta-amyloid (Aβ) peptide is central to the pathogenesis of Alzheimer's disease. Evidence supporting a pivotal role for A includes the following: mutations in the amyloid precursor protein lead to early-onset Alzheimer's disease; all currently known mutations associated with Alzheimer's disease increase the production of Aβ ; in patients with trisomy 21 (Down's syndrome) and three copies of the gene for amyloid precursor protein, neuropathological characteristics of Alzheimer's disease develop by midlife; Aβ is neurotoxic in vitro and leads to cell death; overexpression of human amyloid precursor protein in transgenic mouse models of Alzheimer's disease results in neuritic plaques similar to those seen in humans with Alzheimer's disease; transgenic mice overexpressing the human amyloid precursor protein have evidence of learning and memory deficits, in concert with the accumulation of amyloid; the apolipoprotein E ϵ4 genotype, a major risk factor for Alzheimer's disease, leads to accelerated deposition of amyloid; and the generation of antiamyloid antibodies in humans with Alzheimer's disease seems to ameliorate the disease process [8-12]. Formation of neurofibrillary tangles, oxidation and lipid peroxidation, glutamatergic excitotoxicity, inflammation, and activation of the cascade of apoptotic cell death are considered secondary consequences of the generation and deposition of Aβ. This hypothesized amyloid cascade underlies attempts to modify the onset and course of Alzheimer's disease through identification of antiamyloid agents, antioxidants, anti-inflammatory drugs, compounds that limit the phosphorylation of tau protein, antiapoptotic agents, and glutamatergic *N* -methyld -aspartate–receptor antagonists. Cell dysfunction and cell death in nuclear groups of neurons responsible for maintenance of specific transmitter systems lead to deficits in acetylcholine, norepinephrine, and serotonin [13-14]. Alternate hypotheses regarding the pathophysiology of Alzheimer's disease place greater emphasis on the potential role of tau-protein abnormalities, heavy metals, vascular factors, or viral infections.

CURRENT TREATMENT FOR ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive and debilitating disease that affects many of us, either directly or through someone we know, yet science has still not revealed a cure. Several compounds are being currently tested to prevent and treat the disease. Some current methods of treatment of Alzheimer's disease have been explored [15]. They are as follows:

- **Anti amyloid therapies**

No antiamyloid therapies are currently available. A program to vaccinate humans was implemented after the observation that immunization with Aβ reduces pathological signs of Alzheimer's disease in transgenic mice that have the amyloid precursor protein mutation [16]. This clinical trial was interrupted when encephalitis developed in 6 percent of the patients [17]. Post hoc analyses of a subgroup of 30 patients observed at a single site within the trial suggested that those patients who generated Aβ antibodies had a reduction in disease progression. Passive immunization represents an alternative and perhaps a safer vaccination strategy [18,19]. The enzymes responsible for liberating Aβ, a toxic fragment of 42 amino acids, from the amyloid precursor protein are β and γ secretases. Inhibitors of these enzymes are under active study. The metabolism of cholesterol is intimately involved in the generation of Aβ, and preliminary evidence suggests that statins may be beneficial in reducing the accumulation of Aβ [20]. Metal-binding compounds such as clioquinol may reduce oxidative injury associated with Aβ and may inhibit the aggregation of the Aβ peptide [21]. High blood glucose levels may increase the levels of insulin and insulin-degrading enzymes [22], redirecting the latter from an alternative role in the metabolism of A β. Some investigators suggest that analogues of insulin- degrading enzymes might represent therapeutic options. Strategies aimed at reducing the aggregation of Aβ offer another therapeutic avenue to be explored [23]. The identification of valid targets and potential treatments suggests that disease-modifying therapies will emerge from this research arena.

- **Cholinoceptors Pathway Degeneration [**24-33]

Anticholinergic drugs such as anticholinesterase inhibitors (Rivastigmine, Physostigmine, Neostigmine and Pyridostigmine) has shown good efficacy in improving the cognitive function in Alzheimer type dementia. Their use is limited because of short half-life and systemic cholinergic actions. Amino acridines are playing a vital role in preventing the Alzheimer's disease and its symptoms [34] Tacrine is another anticholinergic drug which inhibits both acetyl cholinesterase and butyryl cholinesterase enzymes which inhibits the effects promoted by M1 and M2 cholinoceptors. Velnacrine, a cholinomimetic analog of tacrine is currently under investigation. Donepezil [35] is another acetyl cholinesterase inhibitor which is presently available.

- **N-methyl-D-Aspartate (NMDA) Pathway Degeneration** [36]

Over stimulation of N-methyl-D-Aspartate (NMDA) produces excitotoxic effects on neurons which further produces neurodegenerative processes. This problem is overcome by treatment with amantadine derivatives such as Memantine (dimethyl adamantine) which is an uncompetitive inhibitor of NMDA receptors.

- **Antioxidants** [37]

The brain has high oxygen consumption rate and abundant poly unsaturated fatty acids in the neuronal cells. If the neuronal cells get free radical damage, it results in cognitive decline and neurodegenerative diseases (Alzheimer's disease). In this case antioxidants such as vitamin-E (α- tocopherol) monoamino oxidase inhibitor (selegiline), [38-39] phenolics (curcumin), tannins (gallic acid) and polyphenolics (ferulic acid) reduce the free radical formation and prevents the cognitive syndromes.

- **Vaccination** [40]

Several vaccines are under development to reduce the cognitive symptoms due to Alzheimer's disease. These vaccines stimulate the immune system to produce antibodies against the pathogens which create the problem. The vaccine is injected in the form of β-amyloid that clear the plaques and physical signs of Alzheimer's disease. One of the developed vaccines administered by intramuscular route is AN-1792 which produces nonfatal inflammation, improvement and recovery from symptoms of Alzheimer's disease. Another one is developed in the modified form of amyloid protein administered by nasal route.

- **Estrogen therapy**

Research work shows that postmenopausal hormone therapy increases the risk of dementia in healthy women. In these circumstances estrogen after administration improves the cognitive function. In this case raloxifene which is a selective estrogen receptor modulator reduces the risk of dementia in Alzheimer's disease (Research approach from University of Wisconsin). The National Institute of aging also prescribed regarding the estrogen patch which is a sustained release to reduce the risks of Alzheimer's disease.

- **Implanting Healthy Neurons**

Cognitive problems are stem from low levels of acetylcholine. Transplanting healthy cholinergic neurons (cholinoceptors) into the brain would be a direct way to restore acetylcholine levels. Stem cells having cholinoceptors is also produce healthy levels of acetylcholine which prevents neurodegenerative diseases (Alzheimer's disease).

- **Support from caregivers** [41].

Spouses are the largest group of care giving. But most of the spouses are older with their own health problems. Hence sons and daughters are the second largest group for take care of them. They are commonly called as "Sandwich Generation" because many are married and raising children of their own. Those children need extra support if a parent's attention is focused on care giving. In that case grandchildren may become the major helpers for them. Daughters-in-law – the third largest group. For the old age people their brothers and sisters are also older and also have their own health problems. The next groups are their friends, neighbors and members of their faith community who are in the same platform.

- **Insulin: (New approach for treatment)**

Insulin and its receptor in the brain have been known to play a very important role in the brain, regulating many key finctions like memory, energy homeostasis, food intake, neurodegenerative disorders and reproduction [42-43]. Insulin plays an important role in memory and other aspects of brain function. Peripheral hyperinsulinemia and insulin resistance induce a number of deleterious effects in the central nervous system that interfere with these functions, in a manner that is exacerbated by obesity and aging. It is likely that insulin modulates memory through diverse mechanisms including effects related to insulin receptor expression, the insulin signalling cascade, cerebral glucose metabolism, neurotransmitter expression, and long-term potentiation. It is not surprising, therefore, that insulin abnormalities have been implicated in cognitive dysfunction. Type 2 diabetes mellitus, chronic peripheral hyperinsulinemia, and impaired glucose tolerance have been associated with impairments in memory and other cognitive functions [44].

Table 1. Clinical Pharmacology of Agents Used Fir Reducing the Signs of Dementia [45]

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3-5	0.5-2	0.5-1	3-7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70-80	2†	5-7	60-80
Protein binding(%)	96	40	0-20	45
Metabolism	CYP2D6, CYP3A4	Non-hepatic	CYP2D6, CYPEA4	Non-hepatic
Dose (initial/maximal)	5 mg daily/10mg daily	1.5 mg twice daily/6mg twice daily	4 mg twice daily/12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyld-aspartate.† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

CONCLUSION

Current therapies for patients with Alzheimer's disease may ease symptoms by providing temporary improvement and reducing the rate of cognitive decline. Given the wide array of available molecular targets and the rapid progress toward identifying potential therapeutic compounds, the development of interventions that substantially delay the onset or modify the progression of Alzheimer's disease can be anticipated.

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