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Review Article

Alzheimer Disease: Therapeutic Targets & Recent Developments in Treatment

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Abstract: Alzheimer's disease is characterised by progressive loss of memory which is episodic in nature. Numerous drugs have been utilised for its treatment like cholinesterase inhibitors, NMDA antagonists etc but none of them have been effective in controlling the disease symptoms & progression. Numerous recent developments have concentrated upon targeting the β amyloid deposition & tau protein deposition in Alzheimer's disease. This review attempts to provide information about the latest targets & developments in treatment of Alzheimer's disease.
Keywords: Alzheimer's, β-amyloid, tau protein, Amyloid Precursor Protein (APP).

INTRODUCTION

Dementia [1] refers to a collection of symptoms resulting from derangement of cognition &/or behavioural brain functions due to diseases & other causes. these include

1. Cognitive symptoms like episodic amnesia, language impairment, visuospatial disorientation, apraxia, impaired attention, calculation & impaired executive functions (judgement, planning, insight, preservation).
2. Behavioural & psychological symptoms (agitation , irritability, anxiety etc)
3. Psychotic symptoms (delusions, hallucinations, illusions, depression, euphoria).

Dementia could be due to reversible causes like meningitis, encephalopathies, neoplasm or irreversible causes like Alzheimer's disease, frontotemporal dementia, dementia with lewy bodies, dementia of Parkinson's disease, vascular dementia etc. Worldwide Alzheimer's disease is one of the leading cause of dementia occurring usually after 65 years of age hence also termed senile dementia[2]. Risk factors for Alzheimer's disease include: Advanced age, Presence of epsilon 4 allele of ApoE (ApoE €4) on chromosome 19,Female gender, Down's syndrome. This risk is further increased by factors like: Low education, Head injury, Hyperhomocystenemia, Family h/o dementia. Decrease in risk is seen with use of NSAIDS & statin therapy.

The two primary pathological hallmarks are[3]:

A. **Amyloid plaques** composed of amyloid β (Aβ), a cleavage peptide derived from amyloid precursor protein (APP/presenilin).
B. **Neurofibrillary tangles (NFTs)** primarily composed of hyperphosphorylated tau proteins.

Nootropics are drugs that improve memory & cognition. Have also been called cognition enhancers. Various nootropics like Piracetam, Aniracetam etc along with vasodilators like co-dergocrine mesylate (dihydroergotoxine mesylate) have been tried but with inconsistent results. Specific drug therapy of Alzheimer's disease have concentrated upon increasing acetylcholine levels in the brain by using cerebroselective cholinesterase inhibitors (ChEI) like Donepezil, Galantamine, Rivastigmine etc. Also efforts have been directed to decrease the excitotoxicity of neurotransmitters like glutamate by blocking the nmda receptors by memantine. However most of these therapies afford only symptomatic relief without any effect on the actual disease progression. Cholinesterase inhibitors have been used in mild to moderate disease while in severe cases memantine has been used in combination with cerebroselective cholinesterase inhibitors for symptomatic relief of alzheimers cognitive symptoms.

However as mentioned earlier the success rate of therapies with these drugs is marginal at best. Hence a review of the presently available therapies is necessary along with emphasis on newer APProaches to treatment of Alzheimer's disease. The newer treatment APProaches in Alzheimer's can be primarily divided into those that focus on anti-amyloid therapies & those that target the tau aggregation pathway along with other alternative therapies.

Pathological mechanisms in Alzheimer's disease:

The widely targeted amyloid deposition in Alzheimer's can be explained by the amyloid hypothesis[4,5] which states that Aβ peptide overproduction/accumulation in plaques due to impaired lysosomal degradation is the underlying cause in Alzheimer's disease. The normal pathway of cleavage of amyloid precursor protein (APP/presenilin) is by nonamyloidogenic pathway where the activities of α,β & γ secretases are balanced, whereas in patients with Alzheimer's the activities of β & γ secretases are in excess of activity of α secretases which leads to imbalance in degradation of APP/presenilin causing release of Aβ peptide into extracellular spaces thus initiating the formation & accumulation of amyloid plaques.

Another widely accepted theory is[6] that hyperphosphorylation of microtubular associated protein tau is responsible for formation of Neurofibrillary tangles which lead to neurodegeneration & cell death in Alzheimer's disease patients.The therapeutic treatment APProaches towards Alzheimer's disease have previously concentrated upon anti-amyloid therapies & recently on prevention of tau toxicity.

The anti-amyloid therapies have focussed on two strategies[7]:

1. Modulate processing of β APP. Eg via β & γ secretase inhibitors [8-13] & by increasing α secretase activity[14].
2. Facilitate clearance of Aβ amyloid via active or passive immunotherapies[15-21].

Secretase inhibitors for β-secretase(bace-1) like grl-8234[8], tak-070[9], e2609[10], mk8931[11] have been under careful monitoring while γ-secretase inhibitors like semagacestat [12] & avagacestat [13] have been tried in various clinical trials with poor success rates because of adverse effects etc. Other strategies have focussed on improving the α secretase activity to ensure adequate degradation of APP like byrostatin-1[14], stazolate & restore the balance among various secretases in patients of Alzheimer's disease.Immunotherapeutic APProaches like passive immunisation with β amyloid monoclonal antibodies (eg bapimuzumab [15,16], solanezumab[17] or active immunotherapy against the Aβ peptide (an-1792[18], cad106[19,20], acc-001[21] have been tried in various clinical trials with several failures due to side effects like acute meningoencephalitis etc.

Tau as a therapeutic target [22, 23]: tau proteins perform the role of stabilising microtubules. They are produced by alternate splicing of gene called microtubule associated protein tau (MAPT). The tau proteins so formed help in microtubule stabilisation by interacting with another protein tubulin. This process is helped by isomers of tau & phosphorylation of tau. In Alzheimer's disease hyperphosphorylated tau is unable to stabilise the microtubules & the helical & straight filaments tangle to form neurofibrillary tangles (NFT's).

Tau serves as a downstream effector of Aβ peptide & its levels have been shown to be increased much before the actual levels of increase in Aβ peptide could be demonstrated. Tau is also subjected to various kinases during its degradation pathway like glycogen synthase kinase 3 [24] (implicated in Aβ production & Aβ mediated LTP (long term potentiation) inhibition.

Among the tau based therapeutic strategies have concentrated upon:

a) **Inhibiting tau hyperphosphorylation**: by use of glycogen synthase kinase-3β inhibitors which prevent phosphorylation of tau into hyperphosphorylated tau eg like lithium [25,26] & tideglusib[27]. Also protein phosphatase 2a (responsibe for dephosphorylation of tau) agonists like metformin & selenium salts have been tried with inconsistent results.
b) **Inhibiting tau aggregation**: by LMTX^{tm}-a methylene blue derivative [28], LMTX^{tm}–tau aggregation inhibitor by inducing oxidation of tau.
c) **Microtubule stabilising agents**: like davunitide (al-108) [29] & epithilome d (hyperphosphorylation releases tau from microtubules & sequestraton of released tau in the neurofibrillary tangles may cause further microtubule destabilisation).
d) **Inhibition of neuronal excitotoxicity**: Aβ peptide causes excessive neuronal stimulation which inturn is dependent on tau. Tau interacts with many kinases one of which is fyn (a serine tyrosine kinase), mislocalisation of tau in Alzheimer's disease causes enhanced post synaptic localisation of fyn & over excitation of nmda receptor-this can be inhibited by antiepileptic drug leviteracetam[30].

Other targets in Alzheimer's disease treatment have focussed upon the below mentioned targets with variable & inconsistent results:

Neurotransmitter Based[7]:

1. ACH based-Huperzine[31].
2. $GABA_B$ antagonists.
3. AMPA Potentiators.
4. MAO A & B Inhibitors.

Anti-inflammatory therapies like nitroflurbiprofen.

Neuroprotection: antioxidants-vit c & e, coenzyme Q10.

Miscellaneous: PPAR γ agonists [32] & insulin etc.

In conclusion the current APProaches towards treatment of Alzheimer's disease have focussed upon anti-amyloid therapies as well as tau based therapies mentioned above with inconsistent benefits along with older treatment strategies like cerebro- selective acetyl cholinesterase inhibitors like tacrine, donepezil, rivastigmine along with other drugs like mementine & galantamine. Behavioural & psychological symptoms are being treated with drugs like quetiapine, olanzapine, risperidone, escitalopram & clonazepam. However these treatments offer far from satisfactory results & further research is required in this area.

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