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Novel therapies for treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population. It is a chronic neurodegenerative disease associated with the loss of nerve cells in areas of the brain that are vital to memory and other mental abilities. Currently available treatments for AD: such as reversible anticholinesterases namely tacrine, donepezil, rivastigmine, galantamine and NMDA receptor antagonists like memantine provide largely symptomatic relief with only minor effects on the course of the disease. There are a number of newer drugs to effectively modify the progression of AD. All of these newer agents are directing towards the biochemical mechanism of AD development, including targeting tau protein (e.g. Inhibition of tau kinase), targeting Aβ (e.g. β-Secretase Inhibitors), and therapies involving gene as well as stem cell strategies. Hence in this review, we summarized the pathogenesis of AD along with the future targets of therapy.

Keywords: Alzheimer's disease, Tau protein, amyloid beta plaques, secretase enzyme

1. Introduction

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population. Dr. Aloysius "Alois" Alzheimer, a Bavarian born German psychiatrist and neuropathologist is credited with identifying the first published case of "presenile dementia", which Kraepelin later identified as Alzheimer's disease.[1]

It has been estimated that ~5% of the population older than 65 years is affected by Alzheimer's disease. The prevalence doubles approximately every 5 years beyond age 65 and some studies suggest that nearly half of the people aged 85 years and older suffer from this devastating disorder.[2]

It is a chronic neurodegenerative disease associated with the loss of nerve cells in areas of the brain that are vital to memory and other mental abilities. The brain region most vulnerable to neuronal dysfunction and cell loss is the medial temporal lobe including entorhinal cortex and hippocampus. Typical early AD symptoms are due to dysfunction of these structures resulting in progressive disturbances of cognitive functions including memory, judgment, decision-making, orientation to physical surroundings and language. Patients present with anterograde episodic memory loss: repeated questions, misplaced items, missed appointments and forgotten details of daily life. [3] Loss of short term memory usually precedes the loss of long term memory. There is reduced verbal fluency and impairment of speech due to failure of arranging words in proper sequence. Ultimately, with progression of brain degeneration, patient may fall in a vegetative state. Death is usually associated with complications of immobility (e.g. pneumonia or pulmonary embolism). [4]

Currently available treatments for AD: such as reversible anticholinesterases namely tacrine, donepezil, rivastigmine, galantamine and NMDA receptor antagonists like memantine provide largely symptomatic relief with only minor effects on the course of the disease.[5]

The ideal therapies for AD should be not only effectively improving the dementia symptoms but also fundamentally reducing the burden of senile plaques and neurofibrillary tangles and thus protect the neurons from degeneration. Currently several drugs and agents that either affect secretory amyloid precursor degradation, or inhibit amyloid peptides aggregation or block hyperphosphorylated tau protein formation are under investigation in preclinical trials. These new approaches are representatives of current therapeutic development for the treatment of AD.[6]

Thus, this article aims at giving a brief account on potential disease modifying drug based therapy that can help modify the pathology of AD as compared to symptomatic therapy.

2. Pathophysiology of AD:[2,3]

The pathological hallmarks of AD are amyloid plaques, which are extracellular accumulations of Aβ and intracellular neurofibrillary tangles (NFTs) composed of microtubule associated protein tau. The current consensus is that Aβ accumulation is an upstream event that triggers tau pathology, resulting in impaired neuronal function and cell loss.

2.1 Amyloid-β (Aβ) accumulation – neuritic plaques

Mutations in three genes have been identified as causes of early onset autosomal dominant AD: APP, which encodes amyloid β precursor protein (APP), and PSEN1 and PSEN2 encoding presenilin1 and presenilin 2. All three genes are involved in production of amyloid β peptides (Aβ). Aβ is generated by sequential proteolytic cleavage of APP by two enzymes, β secretase and γ secretase: the presenilins form the catalytic core of γ secretase. Aggregation of Aβ forms amyloid plaques which cause neurotoxicity.

2.2 Hyperphosphorylated tau protein accumulation - Neurofibrillary Tangles (NFTs)

Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules (MT). A protein called tau stabilizes the microtubules when phosphorylated. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system. Tau pathology develops slowly with increasing age in a large percentage of the population, and this may help explain why age is the major risk factor for AD.[7]

Mechanisms by which Aβ and tau induce neuronal dysfunction and death may include direct impairment of synaptic transmission and plasticity, excitotoxicity, oxidative stress and neuroinflammation.

2.3 Cholinergic hypothesis

The most striking neurochemical disturbance in AD is acetylcholine deficiency.The anatomical basis of the cholinergic deficit is the atrophy and degeneration of the subcortical cholinergic neurons, particularly those in the basal forebrain (nucleus basalis of Meynert) that provides cholinergic innervations to the cerebral cortex.

However AD is far more complex, involving multiple neurotransmitters likes glutamate, 5-HT and neuropeptides and there is destruction of not only cholinergic neurons but also the cortical and hippocampal targets that receive cholinergic input.

3. Target sites for most of the novel drugs in treatment of AD:[6]

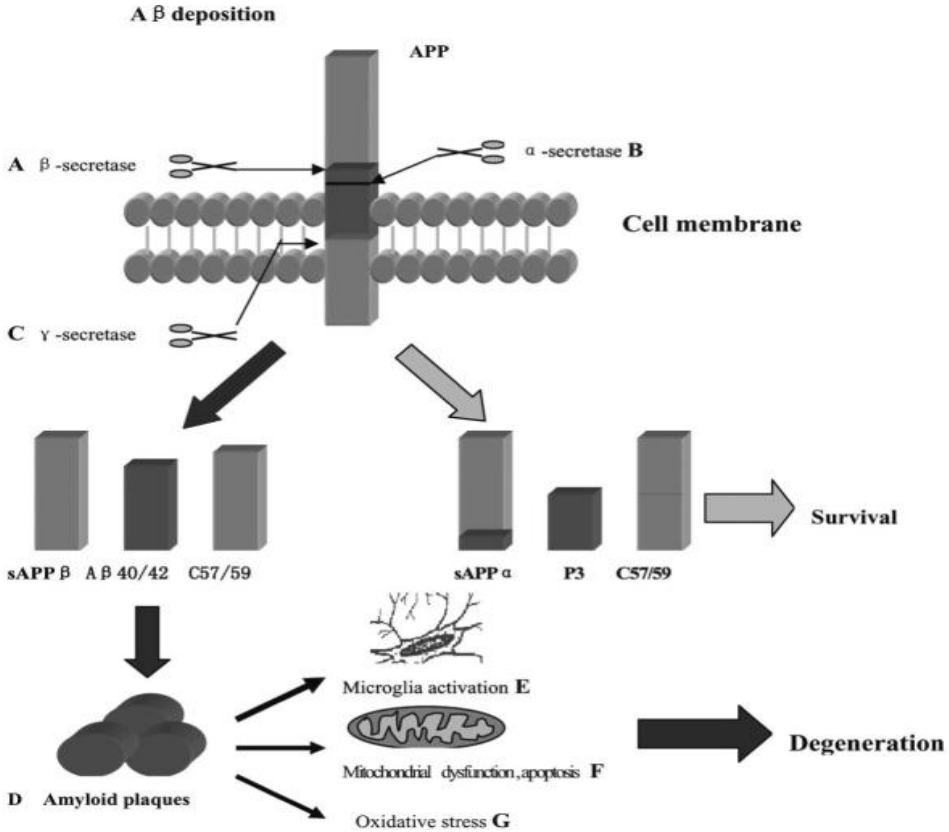

Figure 1: Processing of amyloid precursor protein (APP) and potential therapeutic targets

APP proteolysis undergo two different ways which include hydrolysis catalysed by α-secretase, resulting in release of soluble α-APPs, and the intra-membrane proteolysis catalysed by γ-secretase and produce peptides P3. The second pathway involves β-secretase catalyse which produce β-APPs and Aβ peptides, which ranging in length from 40 to 42 amino acids. Aβ42 peptide is prone to aggregation and formation of amyloid plaques lead to cell degeneration.

Promote activation of α-secretase (**B**) as well as inhibit β-secretase (**A**) and γ-secretase (**C**) are promising targets. Immunotherapies use vaccine or Aβ specific antibodies to promote amyloid plaques degradation (**D**) have been shown safe and effective in animal models. Anti-microglia activation (NSAID) (**E**) Anti-apoptotic approaches and mitochondrial dysfunciton (**F**), and anti-oxidative stress agents (**G)** are benefit in blocking degeneration process.

4. Novel therapeutic strategies

4.1: Targeting Aβ

4.1.1: α-secretase activators:

α-secretase is a member of a disintegrin and metalloprotease (ADAM) family. The initial APP processing involves the cleavage of APP by α-secretase. [8] Because the α-secretase cleavage site is within the Aβ sequence of APP, and none of these proteolytic fragments have been associated with the generation of AD, enhanced cleavage at this site may represent a disease modifying strategy for AD as first postulated by Nitsch and colleagues.[9]

4.1.2: γ-secretase inhibitors:

γ-secretase is responsible for APP proteolysis within the membrane producing the Aβ fragments responsible for forming plaques. γ-secretase inhibitors has provided insights into the proteolytic activity and suggested such inhibition might be a useful therapeutic strategy.

Semagacestat is one such γ-secretase inhibitor used in the IDENTITY (Interrupting Alzheimer's dementia by evaluating treatment of amyloid pathology) trial. It was a randomized, double blind, placebo controlled clinical trial conducted in the U.S and 21 additional countries including 1500 participants for duration of 21 months. On 17 August 2010, it was announced that the phase III trials failed. Preliminary findings show that not only did it fail to slow disease progression, but that it was actually associated with "worsening of clinical measures of cognition and the ability to perform activities of daily living". Also, the incidence of skin cancer was significantly higher in the treatment group than the placebo group.**[**10]

Avagacestat is another such γ-secretase inhibitor which is in phase II trials. It selectively inhibits Aβ synthesis and therefore produces less toxic effects as compared to other drugs from this class.

Tarenflurbil (MPC-7869, formerly R-flubiprofen) is a γ secretase modulator sometimes called a selective amyloid β 42 lowering agent. It is believed to reduce the production of the toxic amyloid β in favor of shorter forms of the peptide. Negative results were announced regarding tarenflurbil in July 2008 and further development was canceled.[11]

4.1.3: β-secretase inhibitors:

Although the development of β-secretase inhibitors has lagged behind the development of γ-secretase inhibitors, many believe that β-secretase is likely to be a better therapeutic target. β-secretase is an important biological target for new drug development, but clinical trials have not yet been conducted.[12,13]

4.1.4: Anti A β aggregation agents

β -sheet breaker that could degrade Aβ is a potential target for AD. This breaker can bind to Aβ and block the interaction between monomers, oligomers and prevent the formation of amyloid fibrils.[14,15]

Numerous enzymes like insulin degrading enzyme (IDE), neprilysin, plasmin etc hydrolyze various peptides with poor substrate selectivity and specificity and thus help in the proteolytic degradation of Aβ. Several anti-Aβ aggregation agents are currently in clinical testing.

Metal ions like Cu2+ and Zn2+ may be involved in the mediation of Aβ aggregation and toxicity. Cu/Zn chelator may help in disintegration of Aβ plaques.

PBT2 is an 8-hydroxy quinoline that removes copper and zinc from cerebrospinal fluid, which are held to be necessary catalysts for amyloid beta aggregation. [16] This drug has been in a Phase II trial for early Alzheimers and which has reported preliminarily promising, but not detailed, results.

4.1.5: Vaccination:

Aβ42 immunization provides effective immune response and promotes amyloid plaques degradation. Immunization with the full-length Aβ42 peptide, containing both B and T cell epitopes, can be more effective in enhancing T cell activation to Aβ clearance. It is desired to have Th2 immune response to promote antibody production and inhibit proinflammatory Th1 response that could activate imbroglio-induced cytokine release and neurotoxicity.

Bapineuzumab is a Humanized monoclonal antibody against Aβ protein. However, various trials failed to produce significant cognitive improvements in patients despite lowering key biomarkers of AD, amyloid brain plaque and phosphorylated Tau protein in CSF. [17,18]

Solanezumab is also a Humanized monoclonal antibody against Aβ protein. Bapineuzumab targets both soluble and aggregated Aβ species, while solanezumab recognizes soluble but not plaque Aβ.Because it does not directly target fibrillar amyloid plaques , Solanezumab was associated with relatively little of the amyloid related edema or haemorrhage that was so evident with the bapineuzumab studies.[19]

4.1.6: Simvastatin, a statin, stimulates brain vascular endothelial cells to create a beta-amyloid ejector.[20] The use of this statin may have a causal relationship to decreased development of the disease.[21]

4.1.7: The endocannabinoid system may have a role in AD.[22,23] For instance, THC, one of the active ingredients in marijuana, has been shown to reduce amyloid beta plaque formation through inhibition of acetylcholinesterase (AChE).[24]

4.2 Targeting tau:

Another pathological hallmark of AD is NFTs, which are composed of intracellular filamentous aggregates of hyperphosphorylated MT-associated tau protein, self-conversion into PHF-tau. Dysfunction of tau proteins is responsible for the failure of the self-assembling tau to regulate the MT dynamics that is essential for cell survival. Tau can be phosphorylated by several kinases including glycogen synthase kinase-3β (GSK3 β) and cyclin-dependent kinase 5 (CDK5) that can be regulated by Aβ deposition.[25-26]

4.2.1: A microtubule-stabilizing drug**, paclitaxel**, had previously been found to improve symptoms of neurodegeneration in a mouse model of tau disease, but it was difficult to deliver the drug to the brain.

4.2.2: Tau kinase inhibitors: Recent studies evaluating the cascade of events leading to neurofibrillary pathology suggest that hyperphosphorylation of tau by kinases such as cdk-5 and GSK-3 is preceded by phosphorylation of the tau microtubule binding domain by microtubule affinity regulating kinase (MARK). It is suggested that inhibition of MARK may block the event(s) triggering microtubule disruption, tau hyperphosphorylation, aggregation, formation of neurofibrillary tangles and neurodegeneration.

4.2.3: It has been suggested, that in Alzheimer's disease, an imbalance of kinase and phosphatase activities may lead to abnormal hyperphosphorylation of tau protein. Activation of phosphatase such as protein phosphatase-2A, may serve as a novel strategy of treatment by promoting the enzymatic dephosphorylation of tau.[27-29]

4.2.4: In July 2008, researchers announced positive results from **methylthioninium chloride (MTC)**, a drug that dissolved Tau polymers. Phase II results indicate that it is the first therapy that has success in modifying the course of disease in mild to moderate AD. [30]

4.3 Cerebroactive drugs:

4.3.1: Brain cell apoptosis inhibitor: Dimebon: Phase II completed. Operates through multiple mechanisms: Blocks the action of neurotoxic beta-amyloid proteins and inhibits L-type calcium channels,[31] modulates the action of AMPA and NMDA glutamate receptors,[32] may exert a neuroprotective effect by blocking a novel target that involves mitochondrial pores,[33] and blocks a number of other receptors, including α-adrenergic, 5-HT_{2C}, 5-HT_{5A}, and 5-HT_6[34]

4.3.2: Nootropic drugs like Piribedil,a dopaminergic agonist; Citicoline, a compound derived from choline and cytidine and Dihydroergotamine, α adrenergic blocking : improve memory, behaviour, concentration and vigilance. They increase cerebral blood flow and are neuroprotective.

4.4 Other therapies

4.4.1: Gene therapy:

Since nerve growth factor (NGF) was discovered to rescue cholinergic neurons from apoptosis in 1986, gene therapy with NGF, glial derived neurotrophic factor (GDNF), brain derived neurotrophic factor (BDNF) and neprilysin for the treatment of AD and related neurodegenerative disorders has been undergoing various experimental and clinical trials. These therapies have been reported not only effective in preventing degeneration of cholinergic neurons but also in ameliorating behavioural deficit and memory impairment in animal models of AD. However, it is a challenge to establish a delivery system that is safe, has high efficacy and is simple.[35,36]

CERE-110 [Adeno- associated virus- NGF (AAV-NGF)]: In Phase 1 clinical trials, it succeeded in stabilizing brain cell metabolic activity. Gene therapy with (AAV- NGF), combined with stereotactic surgery, enables delivery of the gene encoding a biologically active protein such as NGF to a precise location in the brain. The nucleus basalis of Meynert (NBM), a structure near the base of the brain, is considered to be the best target for delivery of a gene-based therapeutic for AD as its cells represent the primary source of cholinergic nerves projecting to the brain cortex. Thus, a single treatment of CERE-110 into this structure is expected to provide a safe long-term source of NGF protein that may protect and preserve cholinergic cells in the brains of AD patients and potentially slow disease progression.[37]

4.4.2: Stem cell therapy:

Neural stem cells, are self-renewing, multipotential cells with the developmental capacity to give rise to all major cells namely neurons, astrocytes, and oligodendrocytes. The development of enzymatic single-cell suspension methods of the fetal brain, initially used for the generation of primary neuronal and mixed glial cultures, enabled the breakthrough discovery that neural stem cells (NSCs) can be isolated from fetal or adult rodent central nervous system tissue and expanded as free-floating cell spheroids called "neurospheres" in the presence of growth factors.[38]

This, together with the action of epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) on stem cell proliferation, results over time in NSC enriched culture. It was suggested that for human neurosphere cultures, besides EGF and FGF-2, the addition of leukemia inhibitory factor further enhances their expansion.[39]

4.4.3: Implant acupuncture

Due to the fact, that the neurotransmitter "acetylcholine" is decreased in these patients, there is evidence, that Implant-Acupuncture is able to increase it. In contrast to conventional acupuncture, Implant-Acupuncture ensures a permanent stimulation on the acupuncture points. This enables the body to harmonize malfunctions continuously and enhances the bodies self-healing potential in a way.

In the past, resolvable catgut filaments were implanted into the skin of the external ear in order to trigger a permanent curing.

Now, titanium needles and bio-resolvable needles are used for implantation. The implant-needle made from medical titanium has only the size of the tip of a pin. It can be implanted directly under the skin with the help of an especially designed device.[40]

4.4.4. Miscellaneous:

4.4.4.1 Antiinflammatory and antioxidant therapies:

Neuroinflammation with overexpression of cytokines is a standard characteristic of the brain pathology present in Alzheimer's disease. Involvement of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) in the pathogenesis of Alzheimer's disease has long been suspected.[41]

The rapid clinical improvement of Alzheimer patients treated with perispinal etanercept provides a new clue for investigating these mechanisms. One suspects that this rapid clinical effect is related to the role of TNF-alpha as a regulator of synaptic mechanisms in the brain.[42] Glia are now known to envelop neuronal synapses in the brain and release molecules, gliotransmitters, which regulate synaptic transmission in those enveloped synapses. TNF-alpha is one of only a handful of recognized gliotransmitters.[43] TNF-alpha released by glia, has been demonstrated to control synaptic strength.[44]

NSAIDS inhibit COX enzymes and thereby decrease the production of cytokines & microglial activation, platelet aggregation, iNOS and beta secretase. Only Ibuprofen and Indomethacin have demonstrated clinical benefit in Alzheimer`s disease. Recent research has found link between antioxidant intake and decreased incidence of Alzheimers thus favouring the use of various antioxidants like Garlic extract , Curcumin ,Ginko biloba ,Vitamin E, A, C, B6, Green tea etc.

4.4.4.2 Anti-infective therapies

The possibility that AD could be treated with antiviral medication is suggested by a study showing colocation of herpes simplex virus with amyloid plaques.[45] Several studies using minocycline and doxycycline, in an animal model of Alzheimer's Disease, have indicated that minocycline [46,47] and doxycycline[48] exerts a protective effect in preventing neuron death and slowing the onset of the disease.

4.4.4.3 Metabolic therapies:

Recent studies suggest an association between insulin resistance and AD (fat cell sensitivity to insulin can decline with aging): In clinical trials, a certain insulin sensitizer called "rosiglitazone" improved cognition in a subset of AD patients;[49,50] *in vitro*, beneficial effects of Rosiglitazone on primary cortical rat neurons have been demonstrated.[51] These PPARγ agonists inhibit inflammatory gene expression, alter Amyloid homeostasis & exhibit neuroprotective effects.

Initial research suggests intranasal insulin might also be utilized - increasing insulin levels in the brain with minimal insulin increase in the rest of the body: Afrezza, a New Inhaled Insulin, Is Approved by the F.D.A.[52]

Allopregnanolone is a hormone recently shown to promote neurogenesis that reverses cognitive deficits, reduce brain pathology, and improve cognition in Alzheimer's model mice. Its levels decline in the brain in old age and AD.[53,54]

5. Conclusion

Patients who are diagnosed today have a number of treatments available, including medication, hormone replacement therapy, alternative medicines etc. None of these treatment options have proven to be fully effective, and not

all of them will provide results for every patient. Despite all the research and investment, currently there is no cure for AD, available treatments offer relatively small symptomatic benefit but remain palliative in nature.

New and more durable disease-modifying treatments are needed. The widespread acceptance of the amyloid hypothesis has spurred intense research efforts to identify disease-modifying treatments that interrupt the natural course of Alzheimer's disease by blocking the pathologic processing of APP to Aβ42 or enhancing its clearance or decreasing its toxicity.

Therefore, prospects for the future of Alzheimer's disease treatment are very encouraging. The diversity of different therapeutic strategies being explored in clinical trials offers hope. In the not too distant future, disease-modifying treatments will become the standard of care and serve as the springboard for permanently changing the course of Alzheimer's disease.

Key Messages

There are a number of newer drugs to effectively modify the progression of AD. All of these newer agents are directing towards the biochemical mechanism of AD development. Hence in this review, we summarized the pathogenesis of AD along with the future targets of therapy.

Search strategy and selection criteria:

References for this paper were identified through searches of PubMed from July 2005 to July 2013 with the search terms “Alzheimer’s disease” , “ pathogenesis” , “ tau protein “, “Aβ amyloid”, “neurofibrillary tangles”, “secretase enzymes” ,“tau kinase”, “monoclonal antibodies” and “stem cell therapy”. We reviewed articles published only in English. The reference list was based on originality, impact and relevance to the broad scope of the review.

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