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Review Article

RECENT ADVANCES INPHARMACOTHERAPY OF ALZHEIMER'S DISEASE

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ABSTRACT

The management of Alzheimer's disease (AD) has been a long-standing challenge and area of interest. Advances in knowledge of the pathogenesis of disease and an increase in disease burden have prompted investigation into innovative therapeutics over the last two decades. Current approved therapies are symptomatic treatments having some effect on cognitive function. Therapies that target β-amyloid (Aβ) have been the focus of efforts to develop a disease modification treatment for AD but these approaches have failed to show any clinical benefit so far. Beyond the 'Aβ hypothesis', there are a number of newer approaches to treat AD. This short review will summarize approved drug therapies, recent clinical trials and new approaches for the treatment of AD.

Keywords: Alzheimer's disease (AD), β-amyloid (Aβ), Tau proteins, Recent advance

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INTRODUCTION

Alzheimer's disease (AD) is a critical neurodegenerative illness characterized by the gradual development of forgetfulness, progressing to disturbances in language, dyscalculia/acalculia, visuospatial disorientation, ideational and ideomotor apraxia, akinesia, and mutism.[1] Epidemiological data show that the occurrence of AD increases with age and doubles every 5 y after 65 y of age.[2-3]There were about 26.6 million cases of AD in the world in 2006 and it is predictable that the worldwide dominance of AD will grow fourfold to 106.8 million by the year 2050.[4]Classical pathological hallmarks are senile plaques, comprised principally of amyloid-b (Ab), and neurofibrillary tangles which consist of phosphorylated tau as shown in fig. 1 and 2.

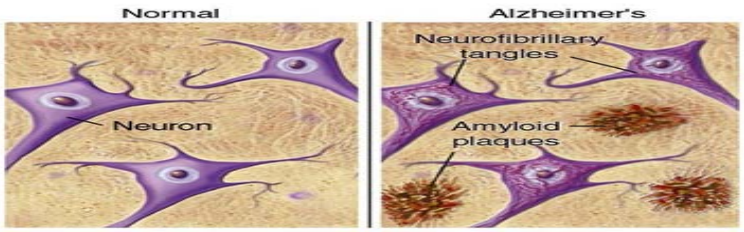

Fig. 1: Microtubules transport nutrition and other molecules

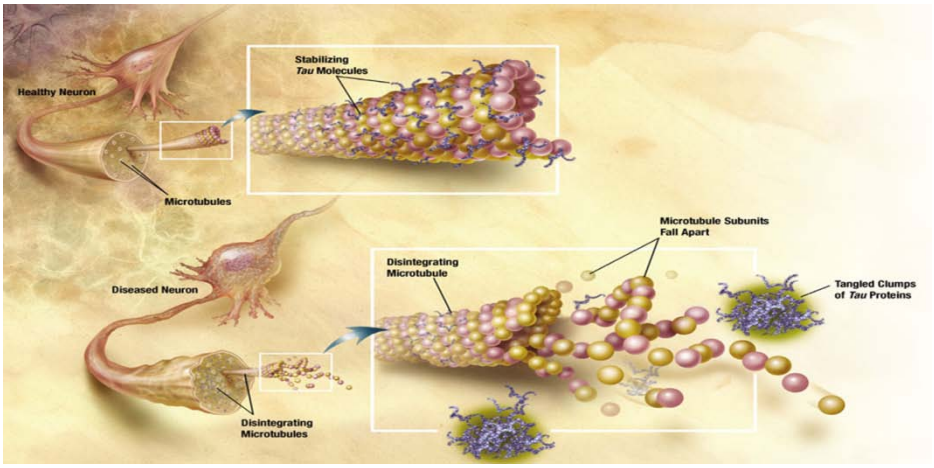

Fig. 2: Microtubules transport nutrition and other molecules. Tau-proteins act as "ties" that stabilize the structure of the microtubules. In AD, tau proteins become tangled, un-stabilizing the structure of the microtubule

These two hallmark lesions are the basis for standard neuropathological criteria for AD, including the Consortium to Establish a Registry for Alzheimer's disease (CERAD), National Institute on Aging-Reagan, and Braak criteria. [5-6]The proposed pathogenic mechanisms for AD generally comprise the basis for current attempts at therapeutic intervention. These include loss of cholinergic function (cholinergicreplacement therapy and neurotropins), oxidative stress (antioxidant therapy), the amyloid cascade (Ab vaccine, bandg-secretase effectors, statins), inflammatory mediators (NSAIDs), steroid hormone deficiencies (hormone replacement therapy), excitotoxicity (memantine), and the role of dietary factors (low saturated fat diets, moderate alcohol intake) as shown in table 1.

Table 1: Showing current treatment of Alzheimer disease based on pathogenic mechanism

Pathogenic mechanism	Treatment
Cholinergic deficiency	Cholinesterase inhibitors: 1st generation: Tacrine 2nd generation: Donepezil, Galantamine, Rivastigmine (patch), NGF gene delivery, Butyrylcholinesterases
Oxidative stress	Alpha-tocopherol, Selegeline
Amyloid cascade	Statins, Secretase effectors
Inflammation	NSAIDs
Excitotoxicity	Memantine
Other	Mediterranean diet

Why is there need for new drug?? Because current treayment

- Do not address underlying pathology of AD
- Positive benefits are relatively short term
- No treatment to reverse, stop or slow neurodegenerative process
- None of the drugs have disease modifying effects that can halt the progression of disease and stop cognitive decline

New targets and compounds for treatment of Alzheimer disease are shown in table 2:

Anti-amyloid therapy

Anti-amyloid therapy involves the uses of drugs (see in table 2) with a different mechanism of actions: (i) enhance the clearance of Aβ; (ii) Prevent the production of Aβ; or (iii) Inhibit the accumulation of Aβ [11]. Active and passive immunization results in decreased levels of intracerebral Aβ burden by inducing humoral reaction against the Aβ peptide leading to its clearance from the brain [12].

γ-Secretase inhibitors (GSI) and modulators (GSM)

γ-secretase is a trans membrane protease responsible for cleavage of amyloid precursor protein (APP) to produce Aβ. Different GSIs such as DAPT, L685458 andMRK-560 131 have been recently developed [13]. While different (GSM) such as avagacestat (BMS-708163), begacestat and NIC5-15 are under clinical trials.

Therapy for mitochondrial dysfunction

Latrepirdine (DIMEBON), an antihistamine which preserves mitochondrial structure and function and protects against A□□ induced apoptosis is under investigation. Its combination with donepezil is also under investigation. AC-1204 is considered to improve mitochondrial metabolism by inducing chronic ketosis, thereby releasing regional cerebral hypometabolism presented in early Alzheimer's disease, and this agent is also under investigation [14].

Table 2: Showing new targets and compounds [7-10]

Compound	Target/Treatment	Current phase
ANI-1792	Vaccine-active immunization	Interrupted at phase I (severe side effects such as meningoencephalitis)
CAD-106	Vaccine-active immunization	Phase I (ongoing)
Bapineuzumab	Beta-amyloid monoclonal antibody	Phase III (ongoing)
Solanezumab	Beta-amyloid monoclonal antibody	Phase III (ongoing)
Ponezumab	Beta-amyloid monoclonal antibody	Interrupted at phase II (no efficacy)
Gantenerzumab	Beta-amyloid monoclonal antibody	Phase I (ongoing)
Crenezumab	Beta-amyloid monoclonal antibody	Phase I (ongoing)
Semagacestat	Gamma-secretase inhibitor	Interrupted at phase III (no efficacy and risk for skin cancer)
Avagacestat	Gamma-secretase inhibitor	Phase II (ongoing)
GRL-834	Beta-secretase inhibitor	Ongoing
TAK-070	Beta-secretase inhibitor	Ongoing
CHF-5074	Non-steroid anti-inflammatory agent	Ongoing
DAPT	Prototypal Gamma-secretase inhibitor	Ongoing
Curcumin	Anti-amyloid aggregator	Ongoing

Kinase inhibitors

The first class of tau inhibitors which helps in targeting tau phosphorylation and reduces tau phosphorylation by decreasing the activity of kinase enzyme. Interaction between glycogen synthase kinase 3 beta (GSK3$\beta\beta$) and protein phosphate 2 (PP2A) augments tau hyper phosphorylation and NFT generation. Lithium, valproate, NP-031112 (NP-12) and epothilone D (BMS-241027) decreases tau phosphorylation and prevent reversed features of tauopathy [15, 16].

$\beta\beta$-Secretase (BACE1) inhibitor

Beta-site APP-cleaving enzyme 1 (BACE1) is a protease responsible for cleavage of APP, resulting in generation of assembly of neurotoxic irregular A$\beta\beta$. Nuclear peroxisome proliferator activated receptor gamma (PPAR$\gamma\gamma$) functions as a transcription factor which regulates gene expression promotes microglia-mediated A$\beta\beta$endocytosis. Also it reduces inflammation response and causes decreased cytokine excretion. Thiazolidinedione can induce PPAR$\gamma\gamma$ to inhibit $\beta\beta$-secretase and stimulate ubiquitination to worsen amyloid burden. It has been also reported that PPAR$\gamma\gamma$ agonist i.e. thiazolidinedione derivatives like rosiglitazone and pioglitazone worsens AD neuropathology by reducing insulin sensitivity which helps in A$\beta\beta$proteolysis [17].

Anticholinergic therapy

Anticholinergic therapy includes administration of cholinesterase inhibitors to treat the cholinergic deficit associated with AD. The

drugs include tacrine (COGNEXS), donepezil (ARICEPTS), rivastigmine (EXELON), and galantamine (REMINYLS) [18].

Immunotherapy

In the attempt to avoid adverse T cell mediated immune response, many vaccination modalities under current investigation are directed towards the humoral response. Nasal immunization of an AD mouse model with AdPEDI-(Ab1e 6) demonstrated a predominantly IgG1 response and reduced Ab load in the brain. Transcutaneous immunization has also been studied in mice with aggregated Ab1e42 plus the adjuvant cholera toxin. This animal study showed significant decreases in cerebral Ab1e40, 42 levels in the setting of increased circulating levels of Ab1e40, 42 without the side effects of brain T cell infiltration or microhemorrhage [19].

Clioquinol

Metal chelation using clioquinol has been reported in apilot study with 36 patients with AD to reduce the rate ofcognitive loss in a double-blind, placebo-controlled, phase 2 clinical trial Clioquinol's effect in this preliminarystudy is due to its ability to chelate zinc and copperassociated with amyloid plaques. The mobilization andremoval of brain amyloid is believed to be basis of itstherapeutic effect. It was reported that clioquinol canreduce zinc accumulation in neuritic plaques and inhibitthe amyloidogenic pathway in APP/PS1 transgenic mouse brain [20].

Resveratrol

Resveratrol, a red wine polyphenol, is known to protect against cardiovascular diseases and cancers, as well as to promote anti-aging effects in numerous organisms. Some recent studies on red wine bioactive compounds suggest that resveratrol modulates multiple mechanisms of AD pathology. It has been recently suggested that resveratrol can be effective in slowing down AD development. As reported in many biochemical studies, resveratrol seems to exert its neuroprotective role through inhibition of Aβ aggregation, by scavenging oxidants and exerting anti-inflammatory activities [21].

Nicotine

Nicotine is a cholinergic agonist that acts both postsynaptically and pre-synaptically to release acetylcholine,which is an alkaloid derived from the leaves of tobacco plants (Nicotianatabacum and Nicotianarustica). Nicotinic receptor densities are further attenuated in age associated neurodegenerative disorders in the elderly, such as AD. Numerous investigations, both *in vivo* and *in vitro*, indicate that nicotine can enhance neurone survival in response to a range of neurotoxic insults [22].

CONCLUSION

The pathogenesis of AD is a complex process involving both genetic and environmental factors; therefore development of effective disease-modifying drugs is proving to be a difficult task. Herein, we have made an effort to review recent trends in AD. The Current therapies for patients with AD may ease symptoms by providing temporary improvement and reducing the rate of cognitive decline. It is hoped that all these lines of ongoing research, should lead to a deeper understanding of the progressions that happen in the brain of Alzheimer patient to permit us to preclude efficiently their incidence. Thus, we conclude that these categories of drugs discussed in this review can be potentially targeted for research and development for the treatment of AD.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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