Diverse aspect for discovering Anti-Alzheimers drug: A hypothesis

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ABSTRACT

Alzheimer's disease is currently deliberation to be a complex, multi factorial syndrome, unlikely to take place from a single causal factor; instead, a number of allied biological alterations are thought to put in to its pathogenesis. This may clarify why the currently available drugs, developed according to the archetypal drug discovery paradigm of "one-molecule-one-target," have turned out to be palliative. In light of this, drug combinations that can act at different levels of the neurotoxic cascade offer new avenues in the direction of curing Alzheimer's and other neurodegenerative diseases. In similar, a new strategy is promising that of developing a single chemical entity able to amend multiple targets simultaneously. This has lead to a new paradigm in medicinal chemistry, the "multi-target–directed ligand" design strategy, which has previously been successfully exploited at both academic and industrial level.

Keywords: Alzheimers Disease, MTDL, Drug Discovery.

1. INTRODUCTION

1.1. Definition

Alzheimer's malady (AD) is the most widely recognized sort of dementia. "Dementia" is an umbrella term portraying a mixture of illnesses and conditions that create when nerve cells in the mind (called neurons) kick the bucket or no more capacity ordinarily. The passing or breakdown of neurons reasons changes in one's memory, conduct and capacity to think plainly. In AD, these brain changes eventually impair an individual's ability to carry out basic bodily functions like walking and swallowing. AD is ultimately fatal[1].

1.2. Prevalence

According to Alzheimer's disease International, about 44.4 million peoples with dementia were estimated worldwide in 2013. This statistic will increase to a level of 75.6 million in 2030 and 135.5 million in 2050. By now, 62% of the populace with dementia survives in developing countries and expected to reach 71% by 2050. The fastest augmentation in the aged populace is taking place in China, India and their other south Asian & western Pacific neighbours.

Demographic ageing is a worldwide process that demonstrates the achievements of enhanced social insurance throughout the most recent century. Numerous are presently living longer and healthier lives thus the world populace has a more prominent extent of more seasoned individuals. Dementia principally influences more established individuals, albeit there is a developing familiarity with cases that begin before the age of 65. There are 7.7 million new cases of dementia every year, suggesting that there is another case of dementia some place on the planet like clockwork [2].

1.3. Current treatment of Alzheimer's disease

At present there no cure for AD, however there are different medications that have been demonstrated to moderate disease progression and treat indications. Treatment of cognitive symptoms includes changing the impact of chemical messengers in the brain. The Food and Drug Administration (FDA) has approved two sorts of medicine for this reason. The principal sort is known as a cholinesterase inhibitor, which upsets the enzyme in charge of the breakdown of acetylcholine in the brain. Acetylcholine is an essential neurotransmitter involved in learning

and memory. Normal aging causes a slight abatement in acetylcholine focus, bringing on intermittent absent mindedness. However, in AD, the focus can be diminished by as much as ninety-percent, bringing about critical memory and behavioral decrease. The function of these medications is to bolster communication between nerve cells, in this manner expanding the concentration of acetylcholine. There are three cholinesterase inhibitors generally endorsed: donepezil, galantamine, and rivastigmine.

In addition to cholinesterase inhibitors, a medicine called memantine has additionally been approved for the treatment of AD. Memantine manages the action of glutamate in the brain. Glutamate is an excitatory neurotransmitter involved in learning and memory[3]. Overstimulation of nerves by glutamate may be the reason for the neuron degeneration found in AD, called excitotoxicity. Glutamate ties to N-methyl-D-aspartate (NMDA) receptors on the surface of brain cells. Memantine works by hindering the NMDA receptors and consequently shielding the nerves from unnecessary glutamate incitement[4]. Memantine is indicated in the treatment of moderate to serious AD and can incidentally defer declining of cognitive symptoms. List of approved drugs for treating Alzheimer's was given in table 1.

\	Table - 1: List of Drugs approved by FDA for AD treatment		
Drug Name	**Condition**	**Action**	**Dose**
Donepezil Brand Name: Aricept	Mild to severe AD	Prevents the breakdown of acetylcholine (ACh) by inhibiting the action of acetyl cholinesterase and treats cognitive symptoms of AD	5 mg taken once per day Over time, may increase to 10 mg daily
Galantamine Brand Name: Razadyne	Mild to moderate AD	Prevents the breakdown of acetylcholine and stimulates receptors to release excess ACh and treats cognitive symptoms of AD	4 mg taken twice daily Over time, may increase to a maximum of 24 mg per day
Rivastigmine Brand Name: Exelon	Mild to moderate AD Also used to treat dementia from Parkinson's disease	Prevents the breakdown of acetylcholine by inhibiting the enzymes that degrade ACh and treats cognitive symptoms of AD	1.5 mg taken twice per day Over time, may increase to a maximum of 12 mg per day
Memantine Brand Name: Namenda	Moderate to severe AD	Blocks glutamatergic (NMDA) receptors and regulates the action of glutamate and treats cognitive symptoms of AD	5 mg taken once per day Over time, may increase to a maximum of 10 mg per day

1.4. Need for new drug discovery for the treatment of Alzheimer's disease:

Most of the drugs that enter the drug development pipeline for AD have failed; since 2004 one agent (memantine) has been approved. 99.6% drugs have been failed since 2002 (with the exception of agents currently in Phase 3). At present 108 trials for AD have been carried out in which 94 agents are unique. A small number of agents in Phase 1 (22) is worrying, in particular, because it indicates that a relatively small number of drug intervention in the process of drug development. Repurposed agents may enter the pipeline at a later stage, but it is unlikely that a large number of agents and will be re-evaluating their use. AD- pipeline of drug development is relatively small, and the rate of success is limited clinical trials of AD. A critical need exists to expand the quantity of agents entering the pipeline and advancing effectively toward new treatment for patients with AD.

1.5. Diverse aspect for discovering anti-Alzheimers drug

1.5.1. Multi-target Drug therapeutics

The fact that complexity and multiple etiologies of AD make single-target strategy difficult to shed desirable therapeutic effect makes the choice of Multi-Target-Directed Ligand (MTDL) to be a potentially more effective strategy.

MTDL, whose goal is to enhance efficacy and improve safety, is rationally designed to hit multiple targets for a particular disease to improve pharmacological profiles. Until now, most drugs approved for AD treatment are AChE inhibitors, which improve the ACh level in the brain by decreasing the hydrolysis of ACh. Amyloid- β (Aβ), formed by the continuously proteolytic processing of β -amyloid precursor protein (APP) by β and γ-secretase, plays a central role in the pathogenesis of AD. Recent evidence indicated certain links between Aβ and AChE. On one hand, the presence of Aβ increases AChE activity, and on the other hand, AChE could form a complex with Aβ, which changes the conformation of Aβ and then promotes the aggregation Aβ. Thus, simultaneously inhibition of AChE and β - secretase (BACE 1) not only reduces Aβ generation and hydrolysis of ACh but also weakens the interaction between ACh and Aβ.

It is critical to recognize, however, that combining two or more drugs always raises the potential for greater side effects. These may include the known side effects of each drug, or completely unexpected side effects caused by interactions between the respective drugs. Another therapeutic option is now emerging, based on the paradigm that a rationally designed, single molecule may possess multiple concomitant biological properties. Clearly, therapy with such a single multimodal drug would have inherent advantages over combination therapy. Such therapy would prevent the challenge of administering multiple single-drug entities that could have different bioavailability, pharmacokinetics, and metabolism. Furthermore, in terms of pharmacokinetic and toxicological optimization, the clinical development of a drug able to hit multiple targets should not, in principle, be different from the development of any other single lead molecule. This therapy thus offers a far more simple approach than combination therapy. In addition, the risk of possible drug-drug interactions would be reduced and the therapeutic regimen greatly simplified, with the prospect of enhanced patient compliance, which is a critical issue in AD care. The development of an effective multimodal treatment is, however, not so clear cut. Neurodegeneration in AD is the result of a several-step process, and addressing with a single drug the molecular dynamics of disease progression is not an easy task. When designing a new chemical entity, one should keep in mind that AD has many stages of progression, and it is crucial to assess the relationship between the progression timeline and a specific molecular target[5-7].

1.5.2. Relation between Alzheimer's disease with oxidants

Inflammatory reactions invariably mean increased production of oxidants, and hence an increased need for antioxidants such as vitamin A, beta-carotene, and vitamins C and E, all of which have been shown to be low in those with Alzheimer's. Other antioxidants, including cysteine, glutathione, lipoic acid, anthocyanidins, and co-enzyme Q10 and melatonin may also prove important.

1.5.3. Relation between Alzheimer's disease with oxidants and microbes

Bacteria and spirochetes are activators of proinflammatory cytokines, generate free radicals, nitric oxide and further induction of apoptosis. Infection with these microbes may be considered as a risk factor for pathophysiology of AD or to cognitive changes. Recent studies have revealed that exposure to these microorganisms induces Aβ accumulation and tau protein phosphorylation, and chronic infections with these pathogenic bacteria can possibly contribute to progression of AD. Intelligent pharmacological approaches including anti-bacterial, anti-oxidant drugs in combination, or drug strategies more effectively directed toward the health and homeostasis of the holobiome should be useful in the future clinical management of AD and related degenerative disorders.

2. CONCLUSION

Multiple, interrelated, biochemical pathways are thought to contribute to the neurodegenerative process of AD. Hence while designing a new drug for the treatment of Alzheimer's disease, researchers can correlate the different biochemical pathways as multi-targeted.and it also can acts as free radical scavengers and neuronal cell protectors to oxidative damage with anti-microbial property. So that the drug can a potent and promising molecule in treating Alzheimer's disease.

3. REFERENCES

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