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Alzheimer's disease Inhibitors: Current status and future prospects

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Abstract

Alzheimer disease is a major public health problem in the elderly. It is the most predominant, intricate neurodegenerative disorder of the brain, affecting above 20 million individuals global. It is an insanity related disease which is characterized by t-protein aggregation, amyloid- β pledges, oxidative stress and lowered levels of acetylcholine in the brain. It is also believed that the plaques and tangles are mainly responsible for the disease. Presently a few class of drugs such as antioxidants, metal chelators, acetylcholinesterase (AChE) inhibitors, monoamine oxidase inhibitors, anti-provocative drugs and NMDA inhibitors present and offer relief. Presently, acetylcholinesterase inhibitors improve the neurological behaviour by increasing availability of acetylcholine at synapse in the presence of intact cholinergic neurons. The genetic studies have revealed four genes that may be linked to the Alzheimer's disease. These four genes include: amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2) and apolipoprotein E (ApoE). When mutation occur in anyone of four genes its lead to the formation of plaques by production of the amyloid beta 40 and 42.Ways to reduce the amyloid plaques and inhibit the action by constructing a drug (1E,4Z,6E)-5-hydroxy-7-(3-hydroxyphenyl)-1-(2-methyl-3,4,4a,8a-tetrahydro-2H-1-benzopyran-8-yl)hepta-1,4,6-trien-3-one and noname 3 as potent inhibitors to PSEN-1 binding domain (aa440).Rivastigmine is a drug which is approved by FDI is mostly used in treatment of Alzheimer disease. It have only two analogues: MOL- I (R=OH) and MOL-III (R=Br) showed good binding energies, low relative free binding energy and high affinities towards AChE in comparison to Rivastigmine. The benefits of specific and selective Alzheimer disease inhibitors are currently under discussion and offer a new perspective for a further development of inhibitors.

Key-Words: Alzheimer disease, AChE Inhibitors

Introduction

Alzheimer (AHLZ-high-merz) is a disease of the brain that causes problems with memory, thinking and behaviour. It is not a natural process of aging. Alzheimer get shoddier over time. Although symptoms can vary broadly, the first dilemma many people notice is forgetfulness severe enough to affect their ability to function at house, at office and to enjoy enduring hobbies. The disease may cause a person to become bemused, lost in familiar places, misplace things and have trouble with language. It is the most common cause of dementia a group of brain disorders that result in the loss of intellectual and social skills. These changes are severe enough to meddle with routine life. In Alzheimer's disease, the connections between brain cells and the brain cells themselves disintegrate and die, causing a steady demur in memory and mental function. Current Alzheimer's disease medications and management strategies may temporarily recover symptoms.

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This can sometimes help individuals with Alzheimer's disease maximize function and maintain independence. But because there is no therapy for Alzheimer's disease, it is important to seek caring services and tap into your sustain network as early as possible.

Alzheimer Affects: The Brain

The changes that take place in the brain begin at the microscopic level long before the first signs of memory loss. What changes occur in the brain during Alzheimer? The brain has 100 billion nerve cells (neurons). Each nerve cell connects too many others to form communication networks. In accumulation to nerve cells, the brain includes cells specialized to support and foster other cells. Groups of nerve cells have unique jobs. Some are implicated in thinking, wisdom and memory. Others help us see, listen and smell. Still others let know our muscles when to move. Brain cells operate like petite factories. They receive supplies, produce energy, construct equipment and get purge of waste. Cells also process and store information and communicate with other cells. Keeping all running requires coordination as well as large quantity of fuel and oxygen. Scientists believe

Alzheimer disease prevents parts of a cell works from running well. They are not sure where the problem starts really. But just like a real factory, backups and breakdowns in one system cause problems in other areas. As smash up spreads, cells lose their capability to do their jobs and, eventually, die.

The Role of Plaques and Tangles in Alzheimer Disease

The brains of individuals with Alzheimer's have a profusion of plaques and tangles.

Plaques are deposits of a protein splinter called beta-amyloid that accumulate in the spaces between nerve cells.

Tangles are twisted fibres of a different protein called tau that builds up inside cells. Though autopsy studies confirm that most people grow some plaques and tangles as they age, those with Alzheimer's tend to grow far more. They also tend to develop them in a knowable pattern, beginning in the areas important for memory before spreading to other regions. Scientists do not know accurately what role plaques and tangles play in Alzheimer's disease. Many experts believe that they somehow play a critical role in jamming communication among nerve cells and disrupting processes the cells need to survive. The damage and death of nerve cells causes memory failure, personality changes, effort in haulage out daily activities and other symptoms of Alzheimer's disease.

Study of Causes of Alzheimer Disease

For the preponderance of patients with Alzheimer disease the cause is unknown, but is likely to represent an amalgamation of genetic and environmental factors. Certainly a main factor is age, with the prevalence just about doubling every 5 years between the ages of 65 and 85 years. Previous risk factors, which have been described above, include Down syndrome (trisomy21), inheriting the e4 allele of the ApoE, or having a first-degree relative with Alzheimer disease. The inheritance of ApoE-e4 seems to promote earlier onset of the disease. It also may modify nongenetic risk factors, such as head injury, which becomes a major risk factor for Alzheimer disease only in persons with the e4 genotype. The ApoE-e4 allele cannot account for all sporadic cases of Alzheimer disease, about 50% of patients with Alzheimer disease develop the disease in the absence of this allele. It is likely that other genes will be identified that modify the development of Alzheimer disease, and that an individual's likelihood of developing the condition will depend on the interaction between inheritance of specific alleles of particular genes and nongenetic exposures. In a small minority of cases in which the disease is familial and inherited as an autosomal dominant trait, a gene defect has been identified as the cause of the disease. All gene defects identified so far lead to lift the production, increased aggregation or perhaps decreased clearance of β-amyloid peptides; this also seems to be true for patients with Alzheimer disease who have inherited the ApoE-e4 genotype. The gradual build up of β-amyloid in brain tissue leads to local microglial and astrocytic activation, and to inflammatory neuronal–neuritic changes that characterize

Alzheimer's disease brain tissue. There appears to be a connection between cerebrovascular disease and Alzheimer's disease. Affected patients often also have cerebral amyloid angiopathy (CAA), which is characterized by deposits of β-amyloid in and around cerebral and meningeal blood vessels. These patients have increased risk of spontaneous cerebral haemorrhage, as well as haemorrhage resulting from trauma and brain surgery. Mutations of APP can lead to CAA or Alzheimer disease, or a mixed phenotype. Further support for a connection between cardiovascular health and Alzheimer disease comes from studies of the ApoE gene. ApoE-e4 is not only a risk factor for Alzheimer disease, CAA and dementia following stroke, but is also associated with high levels of total serum cholesterol, myocardial infarction and atherosclerosis. The lack of a small animal model has hindered the development of treatments or preventive strategies for Alzheimer disease. Advances in genetic studies have led to the development of transgenic mice which express mutant forms of human APP and presenilin. These mice develop age-dependent β-amyloid deposition, but do not show neuronal loss or tangles. When transgenic mice that overexpress APP are crossed with mice that lack ApoE, their offspring show far less β-amyloid deposition than when ApoE is present, suggesting that ApoE may influence aggregation or clearance of β-amyloid peptides. The data from mouse models would indicate that, in addition to abnormal metabolism of β-amyloid, other factors are necessary for the development of Alzheimer disease. The pathology of Alzheimer disease includes inflammatory changes (not seen in the mouse transgenic models) and reactive gliosis by microglia. One hypothesis is that the plaque secretes factors or signals that induce the normally quiescent microglia to interact with the plaque. The activated microglia then produces a variety of neurotoxic substances, which lead to neuronal injury and death. (Nowotny P et al, 2001)

The Discovery of Alzheimer's Inhibitor and its Distribution

Drugs used to indulgence people with Alzheimer's drop into two broad categories:-

- Drugs to cure cognitive symptoms, such as memory problems
- Mental deficits of Alzheimer, and drugs to treat behavioural symptoms that do not react to non pharmacological behavioural. (Gleenon BM et al, 1999).

These drugs might include a diversity of types of drugs broadly categorized as anti-agitation drugs.

AChE Inhibitor

A broad range of facts shows that Acetyl cholinesterase (AChE) inhibitors may impede with the progression of Alzheimer's disease (AD).The successful development of these compounds was based on a well-accepted theory that the demur in cognitive and mental functions linked with AD is related to the loss of cortical cholinergic neurotransmission. The primitive known AChE inhibitors are namely, donepezil, physostigmine and tacrine, showed modest progress in the cognitive function of Alzheimer's patients (Sugimoto H et al, 2000; Preeth M., et al 2010).

Donepezil hydrochloride inaugurates a new class of AChE inhibitors with longer and more discerning action with manageable antagonistic effects. Currently, there are about 19 new Alzheimer's drugs in a range of phases of clinical development. Currently a few class of drugs such as Acetyl cholinesterase (AChE) inhibitors, antioxidants, metal chelators, monoamine oxidase inhibitors, anti-inflammatory drugs and NMDA inhibitors are present and at best they offer some relief of symptoms. But AChE inhibitors like Rivastigmine are the most effective therapy for AD. Rivastigmine is a valuable therapeutic agent for treating cognitive and behavioral symptoms in Alzheimer disease (Farlow RM, 2003; Bourne Y. et al., 2006).

Amyloid Protein Inhibitor

These four genes consist of: Amyloid precursor protein (APP), Presenilin 1 (PS1), Presenilin 2 (PS2) and Apolipoprotein E (ApoE).

In mutation studies it was noted that, when a mutation happens in the APP it leads to the more production of the amyloid beta 40 and 42 which are accountable for the plaques formation .APP is cleaved into alpha-, beta-, and gamma-secretases. Then the study is done on APP protein and ways to shrink the amyloid plaques by constructing a drug by name (1E,4Z,6E)-5-hydroxy-7-(3-hydroxyphenyl)-1-(2-methyl-3,4,4a,8a-tetrahydro-2H-1-benzopyran-8-yl)hepta-1,4,6-trien-3-one,BACE-1inhibitorand inhibit the actions of the amyloid protein.(Vandana S & Barik MR, 2013)

The disease in up to 50% of such cases is explicated by mutations in one of these genes: APP, presenilin 1 (PS1) and presenilin 2 (PS2). Pathological mutations occurs at genes PS1 on Chromosome 14q24.3 and PS2 Genes on Chromosome 1q31-q42.These are conscientious for an autosomal dominant trait and cause α-β accumulation in the brain. We identify noname 3 and noname 1 as potent inhibitors to PSEN-1 binding domain (aa440) (Ahmad J, 2013).

Therapeutics

Classic Alzheimer Inhibitor

Drug Inhibitor ToApp Gene In Alzheimer's Disease

There are four cholinesterase inhibitors (ChEIs) approved by the FDA that helps in blocking the breakdown of acetylcholine. As a result, additional acetylcholine is present in the brain, and it may become easier to form new memories.They are donepezil hydrochloride (Aricept), rivastigmine (Exelon), and galantamine (Razadyne - previously called Reminyl) and tacrine (Cognex). But tacrine has more undesirable side effects than the other three and so is not prescribed by doctors mostly. Several studies suggest that the progression of symptoms of patients on these drugs seems to level for six to 12 months, but inescapably progression then begins again. The recent studies show that even curcumin, commonly known as *haldi* in India, decrease the risk of Alzheimer's disease, as it works as antioxidant, anti-inflammatory, and antitumor. (Hamaguchi T et al., 2010; Ritter JM, 2012).

The Neurotransmitter Acetylcholine (AChE)

Acetyl cholinesterase inhibitors (ACIs) are one of the widely used drugs for the treatment of mild to moderate Alzheimer's dementia. Acetyl cholinesterase inhibitors improve the neurological behavior by increasing availability of acetylcholine at synapse in the presence of intact cholinergic neurons. So identifying classical potent AChE inhibitors are (dimethylamino)methyl ,phenylethyl(methyl)carbamate have been selected as lead moiety. (Paulal A.A.N. de., 2007; Ronco C., 2009).

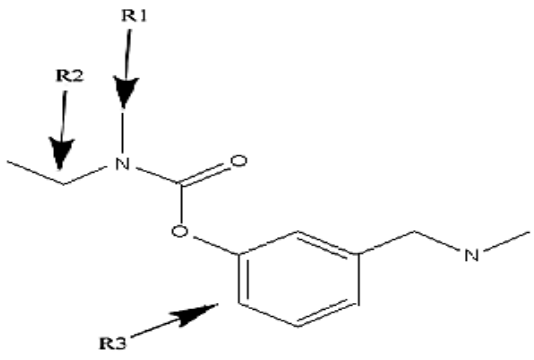


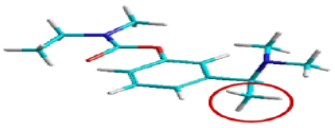
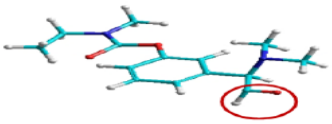
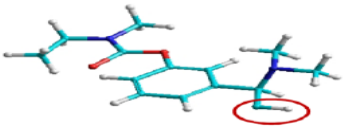
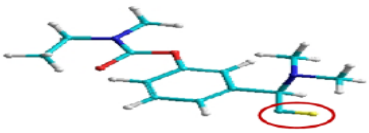
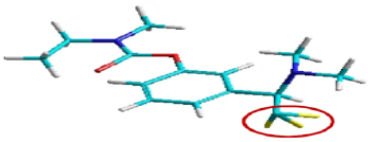
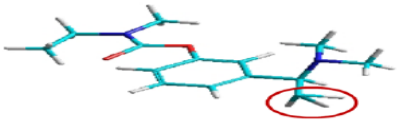
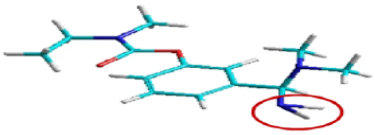
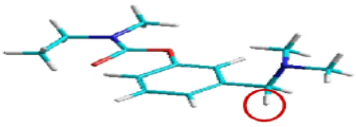
Fig. 1: Positions for the modifications of rivastigmine class of AChE inhibitors (Lead)
(Dutta S. et al 2010; Sandeep Reddy CH. et al 2012)

Modification of Know Alzheimer Inhibitor

Rivastigmine (Golla U. et al., 2013)

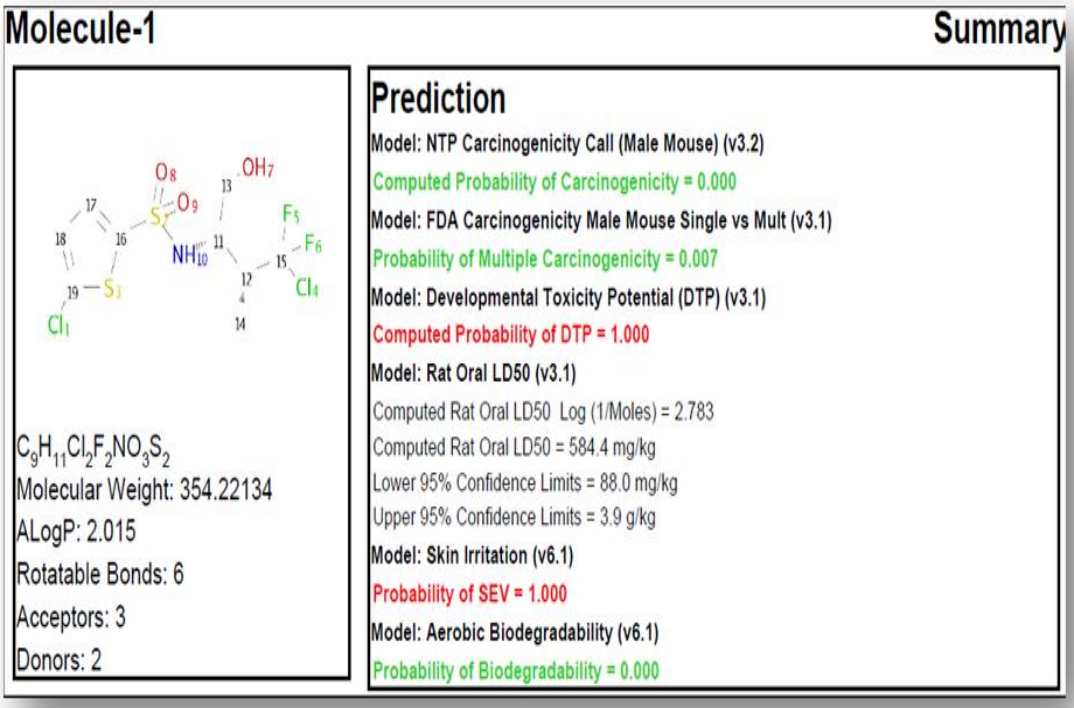
and entire molecule. Also all the Rivastigmine analogues were processed in same way for solvation

Table.1.Rivastigmine and its analogues with their minimized structures

S.NO	Ligand	R- Group	
1	Rivastigmine		CH3
2	Mol- I		OH
3	Mol - II		Cl
4	Mol- III		Br
5	Mol- IV		CF_3
6	Mol- V		CCl_3
7	Mol- VI		NH_2
8	Mol- VII		H

First Rivastigmine has selected and it was optimized gradually like, hydrogen, H2O, part of the molecule process. Solvated molecules Table 1 has given above.

PSEN-1 (Ahmed J.,2013)



Inference: The ligand noname 3 had good TOPKAT score

Cox-2 And New Therapeutic Targets

Angiogenesis – Colon Cancer – Alzheimer's Disease (*AD*)

COX-2 apart from its role in inflammatory sites, COX-2 is involved in numerous physiological and pathophysiological functions. COX-2 is constitutively expressed in the developing kidney and brain, playing an important function in their maturation and function. Additionally, COX-2 expression may be upregulated at certain sites: in the kidney during sodium restriction, in the microglia of cognitive centers inside the hippocampus and cortex in Alzheimer's disease (AD) and in intestinal adenomas and colon tumors. Some details are discussed in the following sections (Lipsky P.E., 1999).The formation of new blood vessels by angiogenesis to provide a blood supply is a major requirement for the growth of many tumors (Masferer J.L. et al., 1999).While mature blood vessels express COX-1, new angiogenic cells articulate inducible COX-2 (Hanahan D. et al., 1996).

In addition to the well recognize peripheral role of COX-2 in inflammation, recent results specify an important role in the central nervous system (CNS). COX-2 is expressed constantly in some excitatory neurons in the CNS. Moreover, expression of this isoform is clearly induced in CNS neurons by excitatory stimuli for example ischemia and seizures so that a role of COX-2- imitative PGs in certain forms of neurodegeneration can be believed. It has also been shown that celecoxib inhibits COX-2 in the CNS at anti-inflammatory doses. Interestingly, application of COX-2 inhibitors to the spinal cord of rats, where COX-2 is also expressed, averts peripheral inflammation and hyperalgesia. Evidently, COX-2 plays an significant role in the CNS in inflammation and pain and it can be deduced that therapeutic consequences of COX inhibitors might be caused not only by peripheral enzyme inhibition but also at least partially by central inhibition. COX-2 in CNS may have an undecided functionality in the brain since the basal production of PGs through COX-2 may contribute in neuronal homeostasis, whereas the expression of COX-2 is associated with brain growth (Halliday G. et al., 2000; Elder JED. et al., 2000). COX-2 is constitutively articulated in neurons and is upregulated in degenerative brain regions in AD such as the microglia of the cognitive centers inside the hippocampus and cortex. Enhanced COX-2 expression in the brain may be associated with beta-amyloid protein accumulation in the neurotic plaques of AD.

This protein and its peptide predecessors are thought to be elaborated as part of an inflammatory cascade in which microglia, a huge source of prostanoids. The role of activated microglia, which express COX-2 in cerebral inflammatory processes, was recently confirmed in the rat (Bauer MKA. et al., 1997).The fact that COX-2 mRNA is elevated in areas related to memory (hippocampus, cortex) and that the amount of COX-2 correlates with the deposition of beta-amyloid protein represents a possible therapeutic benefit and a hopeful new strategy in the prevention or treatment of AD (Dannhardt G. et al., 2001). Despite this interesting and optimistic outlook for future uses of COX-2 inhibitors, most of the findings are based on in vitro and in vivo assays and must urgently undergo investigation in man. (-Bernard MP et al., 2008)

Alzheimer's Disease – The End Of The Story?

Alzheimer disease is the single most common cause of latelife dementia in the industrialized world. The prevalence of the disorder rises with age after the age of 65 years. While some genetic mutations are known to cause a few cases of Alzheimer disease, the aetiology for the vast majority of cases is unknown. It is likely that Alzheimer disease represents the final degenerative pathway initiated by a number of genetic and environmental factors. So far, the most important risk factor seems to be the ApoE-e4 allele, which occurs disproportionately in patients with Alzheimer disease compared with the healthy elderly population.

Treatment of Alzheimer disease slows the cognitive decline to a modest degree, but severe dementia eventually occurs.As yet, there is no treatment that can reverse the effects of Alzheimer disease, and there is no effective prevention. But the new inhibitor drugs of Alzheimer disease:-

- Rivastigmine analogues only two analogues; MOL- I (R=OH) and MOL-III (R=Br) showed good binding energies, low relative free binding energy and high affinities towards AChE in comparison to Rivastigmine.
- Noname 3 as potent inhibitors to PSEN-1 binding domain (aa440). To be more specific about the molecule at the best we recommend ligand noname 3 having most potentiality among all our ligands designed to act as an inhibitors.(Ahmed J., 2013)
- Study is done on APP protein and ways to reduce the amyloid plaques by constructing a drug by name (1E,4Z,6E)-5-hydroxy-7-(3-hydroxyphenyl)-1-(2-methyl-3,4,4a,8a-tetrahydro-2H-1-benzopyran-8-yl)hepta-1,4,6-trien-3-one and inhibit the actions of the amyloid protein.(Vandana S. et al., 2013)
- Donepezil and selected Phytoconstituents with AChE enzyme exhibited binding interactions and warrant further studies needed for the development of potent AChE inhibitors for the treatment of neurodegenerative disorders like Alzheimer disease. (Thimmappa S. et al., 2005)

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