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THE DRUG TARGETING IN ALZHEIMER'S OR APPLICATIONS & ITS HAZARDS

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ABSTRACT

From The era's is the most common from of dementia that is characterised by a progressive decline in cognitive function in brains of Alzheimer's patients. The massive injury and death of neutrons the brain involved In learning and loss of memory called the hippocampus or the spreads to other areas. The although there remains some uncertainty about the mechanism behind disease. Nano technology is advanced form of drug targeting is designed basically for treathment of diseases with the help of nano-particles because they target particular site for an action .The use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under investigation for drug delivery and more specifically for cancer therapy and many more also help in Alzheimer's therapy etc. Interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient. The kind of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in classical delivery matrices etc.

KEYWORDS: drug delivery, Alzheimer's therapy, nanoparticles, toxicology, pharmaceuticals etc.

INTRODUCTION

From The era's serious disease was Alzheimer The Alzheimer's disease accounts for 60 to 80 percent of dementia cases. Alzheimer's is the most common form of dementia, a general term for memory loss and other intellectual abilities serious enough to interfere with daily life.

Alzheimer's is not a normal part of aging, although the greatest known risk factor is increasing age, and the majority of people with Alzheimer's are 65 and older Alzheimer's is not just a disease of old age. Up to 5 percent of people with the disease have early onset Alzheimer's (also known as younger-onset), which often appears when someone is in their 40 year or 50 year also.

Stages of Alzheimer's Disease

Alzheimer's has no current cure, but treatments for symptoms are available and research continues. Although current Alzheimer's treatments cannot stop Alzheimer's from progressing, they can temporarily slow the worsening of dementia symptoms and improve quality of life for those with Alzheimer's and their caregivers. Today, there is a worldwide effort under way to find better ways to treat the disease, delay its onset, and prevent it from developing

- **Symptoms of Alzheimer's**
- **Brain tour**
- **Research**

What is Alzheimer's

Alzheimer's is a type of dementia that causes problems with memory, thinking and behaviour. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks see the fig 1.1.

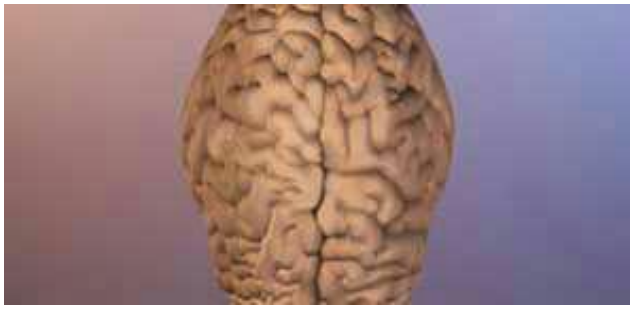

Fig 1.1

Symptoms of Alzheimer's

The most common early symptom of Alzheimer's is difficulty remembering newly learned information. Just like the rest of our bodies, our brains change as we age. Most of us eventually notice some slowed thinking and occasional problems with remembering certain things. However, serious memory loss, confusion and other major changes in the way our

minds work may be a sign that brain cells are failing. The most common early symptom of Alzheimer's is difficulty remembering newly learned information because Alzheimer's changes typically begin in the part of the brain that affects learning. As Alzheimer's advances through the brain it leads to increasingly severe symptoms, including disorientation, mood and behaviour changes; deepening confusion about events, time and place; unfounded suspicions about family, friends and professional caregivers; more serious memory loss and behaviour changes; and difficulty speaking, swallowing and walking. People with memory loss or other possible signs of Alzheimer's may find it hard to recognize they have a problem. Signs of dementia may be more obvious to family members or friends. Anyone experiencing dementia-like symptoms should see a doctor as soon as possible. If you need assistance finding a doctor with experience evaluating memory problems, your local Alzheimer's Association chapter can help. Early diagnosis and intervention methods are improving dramatically, and treatment options and sources of support can improve quality of life.

Brain Tour

The role of plaques and tangles Two abnormal structures called plaques and tangles are prime suspects in damaging and killing nerve cells.Plaquesare deposits of a protein fragment called beta-amyloid (BAY-thud AM-uh-lord) that build up in the spaces between nerve cells.Tanglesare twisted fibbers of another protein called tau (rhymes with "wow") that build up inside cells. Though most people develop some plaques and tangles as they age, those with Alzheimer's tend to develop far more. They also tend to develop them in a predictable pattern, beginning in areas important for memory before spreading to other regions.

Research

Today, Alzheimer's is at the forefront of biomedical research. Researchers are working to uncover as many aspects of Alzheimer's disease and related dementias as possible. Ninety percent of what we know about Alzheimer's has been discovered in the last 15 years. Some of the most remarkable progress has shed light on how Alzheimer's affects the brain. The hope is this better understanding will lead to new treatments. Many potential approaches are currently under investigation worldwide.

Treatment horizon

Many Treatments find that to stop, slow or even prevent Alzheimer's. Because new drugs take years to produce from concept to market—and because drugs that seem promising in early-stage studies may not work as hoped in large-scale trials—it is critical that Alzheimer’s

and related dementias research continue to accelerate. To ensure that the effort to find better treatments receives the focus it deserves fig 1.2.

Fig 1.2

The Alzheimer's Association funds researchers looking at new treatment strategies and advocates for more federal funding of Alzheimer's research.

Factors

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which no cure exists. There is substantial need for new therapies that offer improved symptomatic benefit and disease-slowing capabilities. In recent decades there has been substantial progress in understanding the molecular and cellular changes associated with AD pathology. This has resulted in identification of a large number of new drug targets. These targets include but are not limited to therapies that aim to prevent production of or remove the beta amyloid (Aβ) protein that accumulates in neuritic plaques; prevent the hyper phosphorylation and aggregation into paired helical filaments of the microtubule-associated protein tau; and aim to keep neurons alive and functioning normally in the face of these pathologic challenges. We provide a review of these targets for drug development like Alzheimer's disease, tau- protein, beta-amyloid, A&bita production, immunotherapy Targets for future drugs.

Over the last 30 years, researchers have made remarkable progress in understanding healthy brain function and what goes wrong in Alzheimer's disease. The following are examples of promising targets for next-generation drug therapies are:

1. Inflammation, 2. Tau-protein, 3. Beta -amyloid

Inflammation

Inflammation Is the key Alzheimer’s brain abnormality. Scientists have learned a great deal about molecules involved in the body's overall inflammatory response and are working to better understand specific aspects of inflammation most active in the brain. These insights may point to novel anti-inflammatory treatments for Alzheimer's disea**se.**

Tau-protein

Tau protein is the chief component of tangles, the other hallmark brain abnormality. Researchers are investigating strategies to keep tau molecules from collapsing and twisting into tangles, a process that destroys a vital cell transport system.

Total Tau

Multiple basic science models suggest that reducing tau can alleviate Aβ-dependent or Aβ-independent cognitive impairment in neurodegenerative models. Given that tau is a constitutive part of the cell, however, removing tau entirely is not likely to be a realistic target.

Tau Aggregation

Oligomers of tau are part of normal functioning for the microtubule-associated protein and departure from this oligomeric structure into more aggregated compounds may represent the pathological step in tau processing. Classes of agents that may act to prevent tau aggregation include anthraquinones, polyphenols, amino thienopyridazine, and phenothiazines. Wischik and colleagues have begun clinical development of the phenothiazine methylene blue as a treatment for AD.

Beta- amyloid

Beta-amyloid is the chief component of plaques, one hallmark Alzheimer's brain abnormality. Scientists now have an understanding of how this protein fragment is clipped from its parent compound amyloid precursor protein (APP) by two enzymes — beta-secretase and gamma-secretase. Researchers are developing medications aimed at virtually every point in amyloid processing. This includes blocking activity of both enzymes; preventing the beta-amyloid fragments from clumping into plaques; and even using antibodies against beta-amyloid to clear it from the brain. drug targeting the amyloid pathway in Alzheimer's disease development in fig.1.3

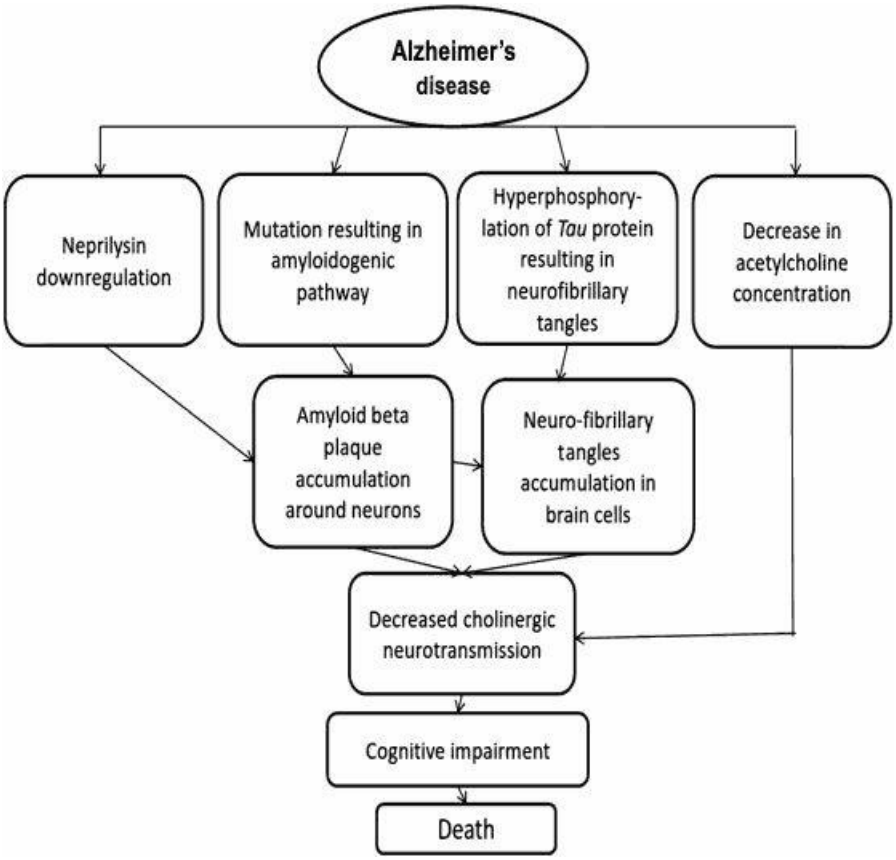

Figure 1.3: drug targeting the amyloid pathway in Alzheimer's disease development.

Aβ Production

Alpha Secretase activation

Increasing production of non-amyloid genic products of APP processing through activation of α-secretase could provide a drug target for reducing pathologic Aβ. Few compounds have been identified that successfully activate α-secretase. Among those that have, receptor agonists for subtypes of muscarinic ACh receptors (mAChR) are appealing. It is clear that among the five different mAChR subtypes, M1is highly expressed in hippocampus and cortex and involved in cognition. Loss of M1function induces cognitive impairment, and agonise of the M1receptor is a logical target for cognitive enhancement.

M1(and M3) receptor agonise also regulates APP processing by increasing α-secretase activity and inhibiting α-secretase It is not yet known if mAChR function in AD is impaired and will limit the efficacy of selective agents that target M1 Treatment of AD patients with an M1agonist, however, reduces CSF Aβ and M1agonists are in development for AD.

Beta Secretase inhibition

Cleavage of APP by BACE (also known as α-secretase and memapsin-2) is the first step in the proteolytic processing of APP, making it the ideal position in the cascade to intervene and halt production of all posttranslational products. BACE activity is increased in sporadic forms of AD BACE knockouts have limited phenotypic changes beyond reduced levels of Aβ suggesting that potent inhibitors may have limited side-effect profiles. Development of agents capable of inhibiting the multisite activity of BACE on its APP substrate has been difficult. Successful inhibition initially required large molecules (>500KDa) that were unable to cross the blood-brain barrier Highly lipophilic, smaller orally available agents that have access to the CNS have recently been developed, however, and such agents are currently in human clinical trials.

Degradation of Aβ

Once present in the brain, the toxic form of Aβ must either be degraded or removed to prevent the clinical development of dementia Multiple endogenous pathways for Aβ degradation exist and include neutral end peptidase (also known as neprilysin) IDE, endothelia-converting enzyme angiotensin-converting enzyme (ACE), and metalloproteinase 9. Of these, neprilysin and IDE are thought to be the primary regulators of Aβ degradation, as well as the optimal drug targets Levels of Aβ degrading enzymes are reduced in AD Further, transgenic animals that lack the proteases key to Aβ degradation show increased brain Aβ deposition in a gene dose-dependent fashion whereas APP transgenic mice that overexpress the neprilysin transgene demonstrate increased Aβ degradation (seen as a reduction in total soluble Aβ and plaque burden) These animals, however, showed no reduction of oligomer Aβ and no improvement in memory performance relative to APP mice.

APP transgenic mice engineered to overexpress IDE and neprilysin have reduced Aβ levels, virtually no plaque formation, and reduced astrogliosis, microgliosis,and dystrophic neurites. These transgenic animals also show improved spatial memory in at least some models Increased levels of neprilysin through viral vector delivered gene expression can lower Aβ in mouse models of AD. Alternatively, molecular regulators of neprilysin levels in vivo could provide a more easily accomplished pharmacologic target. Cabrol and colleagues recently completed a high-throughput screen in which they identified multiple small molecule activators of IDE, suggesting that pharmacological manipulation of Aβ degradation enzymes is a realistic target for disease modification in AD. Given the number of degrading enzymes,

it is important to demonstrate that inhibiting one pathway is adequate for a therapeutic benefit. Alternatively, multiple degradativepathways could be targeted.

Removal of Aβ

Vaccination with the full length Aβ peptide decreases amyloid burden and abrogates learning and memory impairment in animal models of AD. Recent animal model investigations suggest that vaccination can reduce amyloid burden as well as neurofibrillary tangle pathology A clinical trial of Aβ vaccination (AN1792) in 300 mild AD patients was halted due to a 6% incidence of T-cell mediated meningoencephalitis T-cell mediated meningoencephalitis.[132] Preliminary results suggested a clinical benefit in participants who received therapy and generated antibodies against Aβ. Analysis of the primary outcomes at the time of trial interruption demonstrated no drug-placebo difference. Long-term follow up of survivors suggested a benefit in activities of daily living, quantified with the Disability Assessment for Dementia scale, among antibody responders. Long-term follow-up to autopsy of the first subjects to die, however, demonstrated that there was no impact on clinical progression to advanced dementia, despite removal of plaque burden in the cortex among antibody responders. Further, initial pathological analysis suggested that while Aβ removal was successful, NFT pathology was unaltered These findings have sparked continued debate as to whether Aβ provides the appropriate target for AD therapies.

Nevertheless, clinical development of immunotherapies for AD, including active vaccinations, remains a major research focus. Full length Aβ vaccinations, as well as peptide fragment vaccinations, are in development. The initial clinical trial of this agent failed to meet its PR specified endpoints but long-term observations and biomarker studies suggested possible benefit. Clinical developmentin AD continues. Methylene blue also decreases Aβ oligomers in vitroby increasing fibrillar but not monomeric Aβ.

Treatment of Alzheimer's Disease

Alzheimer's disease is complex, and it is unlikely that any one drug or other intervention can successfully treat it. Current approaches focus on helping people maintain mental function, manage behavioral symptoms, and slow or delay the symptoms of disease. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented. Maintaining Mental Function Several medications are approved by the U.S. Food and Drug Administration to treat symptoms of Alzheimer's. Donepezil (Aricept®), rivastigmine (Exelon®), and

galantamine (Razadyne®) are used to treat mild to moderate Alzheimer's (donepezil can be used for severe Alzheimer's as well).Memantine (Namenda®) is used to treat moderate to severe Alzheimer's. These drugs work by regulating neurotransmitters, the chemicals that transmit messages between neurons. They may help maintain thinking, memory, and communication skills, and help with certain behavioral problems. However, these drugs don't change the underlying disease process. They are effective for some but not all people, and may help only for a limited time.Managing BehaviorCommon behavioral symptoms of Alzheimer's include sleeplessness, wandering, agitation, anxiety, and aggression.

CONCLUSION

Alzheimer's disease is a today life in women disease .and Alzheimer disease is a devastating disease and that .courses individuals to less of memories .the relationship and ultimately their lives .family and the caregivers face of many challenge .as the care for a loved one who is gradually slipping away from a societal perspective .and the particularly.an the health care system is the Alzheimer patient grows

The new innovative medicine are needed to treat. slow or prevent Alzheimer s disease.

The biopharmaceutical research companies are studying many potential new.treatment. however. the part from basic research to new drug treatment is extremely long complex with many particularly in the case of Alzheimer's disease from Not proper function of nervous system and brain nerve is proper no Response.

The new analysis develops finds that .the around 1998 to 2014 .there were .123 unsuccessful attempts to develop drugs to treat Alzheimer s and the as some cell then (failures). In the time for me.

The four new medicine .ware approved .about 30 failed to yield a new medicine.

The approach 10 million per year in India cases all of the average in India although .these setbacks are deeply .disappointing .they aften. contribute to eventual success by helping gaide. and redirect the work of scientists investigation new drugs. with the so much to learn. and understand. about the brain and neurological .diseases like Alzheimer's. the research. take the findings from the unsuccessful projects for new medicine.

•but drug is a Attack of nerve cell of brain support of nerve and target of first time in Alzheimer's disease in 90% of successful in drug. and 10% of unsuccessful of drug. but new

drug develop of treat in Alzheimer's disease . from nervous system control (brain) as a nerve cell recovery of nerve cell.

The biopharmaceutical research and the companies they work .for the profoundly .committed to finding treatments of nerve cell the research are currently working on 59 medicines in development for the treatment of Alzheimer's and other Dementia's. they are given patients and free of Alzheimer's disease. Although these setback are deeply disappointing. And Alzheimer's disease.

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