Therapeutic Targets and Challenges during Delivery of Drugs used in Alzheimer's Disease

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Abstract

Alzheimer's disease is most common cause of dementia. The pathophysiology of Alzheimer's disease includes the presence of extracellular plaques of insoluble β-amyloid peptide (αβ) and neurofibrillary tangles (NFT) of P-tau in neuronal cytoplasm. Due to this β-amyloidal plaques and neurofibrillary tangles formation it will damage the neurons and synapses which is involved in memory process can be affected. So, in this review article we will discuss about different therapeutic Targeted for Alzheimer's Disease like anti-amyloidal approaches, anti-tau approaches, acetylcholinesterase inhibitors, glutamatergic system modifiers, immunotherapy, anti-inflammatory targets, antioxidants, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, insulin. There are different Challenge in the Delivery Drugs for Alzheimer's Disease. Also, there are different drug delivery strategies by oral, transdermal, intravenous, intranasal and other miscellaneous route which ultimately leading to Alzheimer's disease cure. By this review we will get better understanding of Alzheimer's disease pathophysiology, therapeutic targets and drug delivery systems towards better delivery of anti-Alzheimer actives.

Keywords: Neurofibrillary tangles, Alzheimer's disease, Dementia, Amyloid β, Tau, Neurodegeneration

INTRODUCTION:

Dementia is the 21st Century epidemic, is one of the most significant health crises impacting families, also it is the social service and healthcare delivery systems.[1] Dementia occurs mostly in people older than 60 years, which may lead to a rapidly increasing in the number of patients causes dementia.[2] Dementia is a clinical syndrome in which there is a progressive decline in two or more cognitive domains, which including memory, language, executive and visuospatial function and behavior, which will lead to the loss of abilities to perform instrumental or basic activities of daily living. Alzheimer's disease (AD) is an ailment that leads to the deterioration of brain cells and is the primary reason for dementia, which is defined by a decrease in thinking and independence in personal daily activities. It is most important problem of medical and social impacting older people. For this condition, there are symptomatic drugs that can correct the neurotransmitter imbalance. [3,4]

- **AD Is the Characterized by Two Types of Lesions:**

1) Senile Plaques:

Composed of a nucleus of β-amyloid protein accumulation (αβ42), as extra- cellular lesion.

2) Neurofibrillary Tangles:

which composed of phosphorylated tau protein (P-tau) and which are intraneuronal. Alzheimer's disease typically consists of progressive memory decline initially, which is accompanied by other cognitive dysfunctions, such as visuospatial abnormalities, navigation difficulties and language disturbance.[4]

- **Risk Factors for Alzheimer's Disease:**

There are sevseral risk factors for AD such as increasing age, genetic factors, head injuries, vascular diseases and environmental factors. The root cause of pathological alterations in Alzheimer's disease (Aβ, NFTs, and synaptic loss) remains unidentified. Several hypotheses were proposed as a cause for AD. [5]

PATHOPHYSIOLOGY:

Alzheimer's disease (AD) is a complex neurodegenerative disorder that affects the brain, leading to progressive cognitive decline, memory loss, and behavioral changes, typically in older adults. The pathophysiology of Alzheimer's is multifaceted, involving the abnormal accumulation of proteins, synaptic dysfunction, neuronal death, and chronic neuroinflammation, all of which contribute to the gradual degeneration of brain function.[6]

At the core of Alzheimer's disease are two key pathological features: amyloid-beta (Aβ) plaques and tau tangles. Amyloid-beta is a segment of protein obtained from the cleavage of amyloid precursor protein (APP). Normally, APP is broken down by enzymes, but in Alzheimer's, it undergoes abnormal processing by β-secretase and γ-secretase, leading to the formation of insoluble Aβ fragments, particularly Aβ42. These fragments clump together to form plaques that accumulate between neurons. These plaques disrupt communication between neurons and trigger an immune response in the brain, which further damages surrounding tissue. [7]

In addition to amyloid plaques, Alzheimer's is also characterized by the formation of neurofibrillary tangles (NFTs) inside neurons. These tangles are composed of hyperphosphorylated tau, a protein that normally stabilizes microtubules, which are responsible for transporting nutrients and molecules within the neuron. In Alzheimer's, tau becomes abnormally phosphorylated, causing it to detach from the microtubules and aggregate into twisted tangles. The accumulation of tau tangles disrupts the cell's internal transport system, leading to neuronal dysfunction and cell death. [7,8]

The progression of Alzheimer's is also driven by neuroinflammation. In response to amyloid plaques, microglia, the brain's resident immune cells, become activated in an attempt to clear the plaques. However, chronic activation of microglia leads to the release of pro-inflammatory cytokines, which exacerbate neuronal damage. The brain's immune system, therefore, shifts from a protective role to a damaging one, amplifying the neurodegenerative process.[8,9]

Another significant contributor to Alzheimer's disease is oxidative stress. The abnormal accumulation of amyloid-beta and tau increases the production of free radicals—unstable molecules that damage proteins, lipids, and DNA. This oxidative damage impairs the normal functioning of mitochondria, the energy-producing organelles in neurons, which further accelerates cell death.[10]

TREATMENT:

❖ **Anti – Alzheimer's Drugs:**

➢ **Acetylcholinesterase Inhibitors:**

In pathophysiology of AD, it observed that there is the cholinergic neuronal death is occurring and it will lead to the ACh imbalance and it associated with cognitive decline. So, if there is restoration of CNS ACh

level then it gives symptomatic relief. Due to cholinergic neuronal death, it restricted the ACh release from neuron and also their restoration in CNS. By using acetycholinesterase inhibitors it will give relief from AD. Marketed Acetycholinesterase inhibitors are tacrine, donepezil, rivastigmine, and glutamine are used for AD. This drug also used to arrest neurogenertion and delay AD progression, if therapy starts at early stage in patient with wild to moderate AD. The mechanism of rivastigmine is that it blocks the butyrylcholinesterase level which give prolong cholinesterase inhibitor activity. Glutamine bind to the nicotinic ACh receptor sites which help to opens the ionic channel and it help to improve receptor response to ACh. Also, acetycholinesterase enzyme enhance αβ plaque formation, so if we use Acteylcholinesterase inhibitors it gives relief symptomatic as well as it arrests the AD progression. [1,2,10,11,12]

- **Amyloid Cascade:**

This Hypothesis was given by Hardy and Higgins in 1990's. This hypothesis is based on formation and accumulation of toxic αβ fragment which will result into abnormal amyloidogenic cleavage of extracellular fragment which will result into cleavage of Trans membrane APP whichwill cause mutation in APP and presenilin gene which used to regulate the entire pathway. It will lead to the insoluble αβ fragment which will further form senile plaques and cerebrovascular deposit occur. Due to toxic in nature result into synaptic loss and neuronal death. There are three enzyme which having important role in natural cleavage of APP these enzymes are α, β, and γsecretase. At first there is cleavage of extracellular fragment take place by using enzyme α-secretaseor β-secretase it will leads to the attachment as 83 or 99 amino acids as a Trans member fragment. Again, this fragment is cleavage by γ-secretase and formation of toxic αβ fragment occurs. By thatway there is initiation of extracellular plaque formation take place. [2,10,11]

- **Alpha secretase stimulator:**

According to the amyloid hypothesis, non-amyloidogenic pathway is promoted by cleavage of APP.The α-secretase help to prevent plaque formation and it also give protection in Hippocampus region.

- **Beta secretase Modulators:**

B-secretase enzyme is used to initiate amyloidogenic pathway. This enzyme producing an Inhibitory activity also it cross the blood brain barrier.

- **γ –Secretase Modulators:**

In Amyloid hypothesis, the amyloidogenic pathway is promoted by APP by BACE 1 and γ-secretase. So, the inhibition of this enzyme has major impact as a therapeutic target**.**

DRUG DELIVERY SYSTEMS FOR ALZHEIMER'S DISEASE:

There are different drug delivery systems are available in case of Alzheimer's Disease.

- **Oral Drug Delivery Systems:**

Oral drug delivery systems are convenient drug delivery systems in AD. Marketed first drug which approved for AD was oral capsule that is Tacrine which is reversible achei. The investigation given towards modified dosage form like achei, metal chelators, polyphenols ect. The polyphenols like (-)-epigallocatechin -3 - gallate used as αlpha secretase that has mechanism to activate nonamyloidogenic process APP but it is poor for oral oral delivery. Smith et al developed nanolipid particle of EGCG at drug to excipient ratio from 1:1 to 1:32. In vitro studies in murine neuroblastoma cell indicated to enhance alpha secresase activity. Another various AD treatment Target are antiprogesteron drug like mifepristone used to arrest cognitive impairments and give symptomatic relief. The current market staus and ongoing clinical investigation for AD therapeutic are given below along with their mechanism of action. [22]

- **Intravenous Drug Delivery Systems:**

In intravenous delivery system it gives 100 % bioavailability in AD. As this drug has High level in systemic level that has High permeation across BBB. The used of nanoparticle carrieracross BBB is used as targeted ligands which understand the potential of Nerve growth factor (NGF) for maintenance of cholinergic neuron. Kurakhmaeva et al used as polybutylcyanoacrylate (PBCA) as nanoparticle of NGF having polysorbate 80 coat which is used as targeted ligands across BBB. Intravenous immunoglobulin is use in AD as it contains Anti - αβ antibodies, it is in under study for their therapeutic assessment.[23]

- **Intranasal Drug Delivery Systems**:

By considering nasal epithelium and olfactory pathways, nanoparticle medicated transdermal patches are used as a intranasal drug delivery for treating AD. Olfactory pathways bare recommend as comprehensive toward brain delivery. Due to advantage like mucoadhesion, negligible nasal irritation the natural polymeric nanocarriers via albumin are explored as nanoparticle. Nanospheres of Tacrine used which is coated by bovine serum albumin using coacervation technique. This nanoparticle has mucoadhesion property. Nasal mucosa gives 100 min permeation and it has clearance time approximately about 4 br. Their different research has been developed in nanoemulsion based anti - AD drug. Nanoemulsion of Curcumin has hydrophilic lipophilic balance surfactant with 100 nm size. [21,22]

The nasal route efficacy towards therapeutic actives is well perceived with clinical studies which is performed for insulin dely in patients with AD. So, insulin delivery is via nasal route. There is also further study given for attension and memory improvement in which insulin pathway has important role.[23]

- **Transdermal drug delivery systems:**

For long term treatment Transdermal drug delivery systems is ideal system for AD which give prolong effect with reduced dosing frequency. Also, it used when there is problem with oral dosage form like side effects, first pass metabolism, etc. First AChE inhibitor drug rivastigmine is used in form of transdermal patch which in Market at 2007. Also, various conventional patches used for AD therapeutic, further to enhance Permeability across skin, technology are used like iontophoresis, sonophoresis are investigated which use to treat AD. [22]

Transdermal drug delivery systems (TDDS) offer a promising avenue for treating Alzheimer's disease by providing a non-invasive route for delivering therapeutic agents that can enhance brain function. Traditional methods of drug administration, such as oral or intravenous routes, can be hindered by the challenges of achieving adequate drug concentrations in the central nervous system due to the blood-brain barrier. TDDS can facilitate a steady, controlled release of medications like cholinesterase inhibitors or novel neuroprotective agents through the skin, potentially improving patient compliance and minimizing side effects associated with fluctuating drug levels.[23]

CHALLENGES FOR AD THERAPY:

Despite intension investigation of mechanism of AD pathogenesis during past three decades, for acheived effective treatment to prevent or cure AD. The amyloid casade hypothesis has been dominated research for past 20 yr, it shifts towards disease modifying drug dei in last decade that might to develop underlying Disease process. At earliest stage neuroinflammatory factor support vicious cycle of microglial activation, it releases inflammatory factors and causes neuron damage. In addition to this inflammatory mechanism such as TNF alpha have orchestrated between brain and periphery, it provides link between AD and peripheral metabolic deregulation.[24]

Therapeutic approaches with intravenous immunoglobulin and monoclonal antibodies are currently under

evaluation but results have not been conclusive yet. This uncertain result has some extent due to anti-inflammatory drug target genetic rather than neuroinflammatory compentent in AD. The modulators of inflammatory at Disease stage will be important to understand the potential of targeting inflammation in neurogeneration.[25]

FUTURE PROSPECTS:

Future treatment of AD involves targeting to the neurofibrillary tangles and senile plaques. There remains debate as abnormality is best target to slow neurologic decline as well, we Treatment is soon. Also aimed to fortify transcortical network to enhance intra neuronal connection for enhancingcognitive function. Clinical trials are underway so to aim to treat AD. Some of challenge identifiedas difficulty in predicting success which based on study for certain drug and overall cost for clinical trial in large scale. Neurodegeneration is the primary pathophysiological cause of Alzheimer's disease. Stem cell induced neurogeneration which will not only arrest disease but also it gives symptomatic relief. Mesenchymal stem cell augmented neuronal cell differentiation, resistance to tauopathy.

Therapeutic Targets and Challenges in Drug Delivery for Alzheimer’s Disease" highlights the complexity of addressing this neurodegenerative disorder. While promising therapeutic targets such as beta-amyloid plaques, tau proteins, and cholinergic pathways offer potential, significant challenges remain in drug delivery due to the blood-brain barrier (BBB), systemic toxicity, and limited drug bioavailability. Advances in nanotechnology, biomaterials, and targeted delivery systems are pivotal in overcoming these obstacles. Continued research and innovative approaches are essential to develop effective, patient-centric treatments for Alzheimer’s disease.

CONCLUSION:

In this review we discussed about pathophysiology of Alzheimer's Disease in which it contains how Alzheimer's Disease occurs due to formation of senile plaques and neurofibrillary tangles formation AD caused. Bue to senile plaques and neurofibrillary tangles it caused neuronal death and so many complications are occurring in patient suffering from AD. So based on that there are many hypothesesare given. It also includes various therapeutic targets which helps to treat AD. Therapeutic targets included Anticholinesterase inhibitor, it inhibits enzyme cholinesterase which help to increase Acetylcholine level in synapse. Then next therapeutic targets are α-secretase stimulators, β-secretase modulators, γ-secretase modulators which inhibit formation of αβ senile plaques which is important caused of AD. Inhibitors of αβ aggregation also used as Targeted Treatment AD. Then this review also includes Tau-targeted therapeutic, Glutamatergic system modifier, Antioxidants for AD therapy, Inhibitors of αβ aggregation help in treating AD. Then at last review include challenges and feature aspect for Alzheimer’s Disease.

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