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Review Article

Review on Study of Nanoparticles in Brain Targeting for Treatment Of Alzheimer's

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Abstract

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, in which there is a progressive deterioration of intellectual and social functions, memory loss, personality changes and inability for self-care, and has become the fourth leading cause of death in developed countries. Pathogenesis of AD, there is a progressive deposition of *β*-amyloid (A*β)*- peptide in the hippocampal and cerebral cortical regions. This deposition is associated with the presence of neurofibrillary tangles (NFTs) and senile plaques. The senile plaquesdeposited between the neurons consist mainly protein *β* amyloid. Neurofibrillary tangles deposited inside the neurons fabricated from *Tau* protein. Diagnosing Alzheimer's requires careful medical evaluation thorough medical history, mental status testing, physical and neurological examination tests (such as blood tests and brain imaging), two classes of medications approved to treat AD. Cholinesterase inhibitors: Donepezil, Rivastigmine, Galantamine, NMDA receptor antagonists: Memantine. The major goal in designing nanoparticles as a delivery system are to control particle size, surface property and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutic optimum rate and dose regimen of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Many strategies have been developed to deliver the drug into brain by crossing the BBB: chemical delivery systems, magnetic drug targeting or drug carrier systems such as antibodies, liposomes or nanoparticles. Among those, nanoparticles have got a great concentration as the potential targeted drug delivery systems in the brain recently.

Keywords: Alzheimer's disease, *β*-amyloid, cholinesterase inhibitors, Curcumin nanoparticles.

Introduction

Alzheimer's disease: Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, in which there is a progressive deterioration of intellectual and social functions, memory loss, personality changes and inability for self-care, and has become the fourth leading cause of death in developed countries[1, 2].

Alzheimer's disease (AD) is a neurological condition that progressively affects neurons and causes irreversible dementia syndrome. The incidence of AD grows with age and is more common in older people. It currently affects 32.6 million people worldwide, but without new treatments, it is expected to nearly double every 20 years, reaching 78 million by 2030 and 139 million by 2050. It causes a decline in behavioral, mental, and other intellectual abilities. It leads to the death of brain cells, which causes memory loss. AD is a neuropathological disease caused by the extracellular aggregation of amyloid beta (Aβ) plaques and the accumulation of intraneuronal neurofibrillary tangles of tau (τ) protein. Aβ is developed by the division of type I membrane proteins, such as amyloid precursor protein (APP), and is present at significant levels in the patient's cerebrospinal fluid and plasma. Therefore, depletion of Aβ plaque deposition and inhibition of p-τ fibrils is involved in the dual-target therapy for AD. It is an uncurable disorder and does not have specific diagnostic approaches or therapeutic drugs. The therapeutic agents presently known for AD only reduce the symptoms. The current course of treatment enhances cognitive abilities and temporarily relieves symptoms, but it does not halt or slow the disease's development. Additionally, treatments are primarily offered in conventional oral dose forms, and conventional oral treatments lack brain specialization and cause adverse effects, resulting in low patient compliance.[3]

Etiology: Although the etiology of the disease is still unclear, many factors are thought to play a crucial role in its pathogenesis, among them oxidative stress, abnormal proteins and excessive metal ion accumulation in brain and reduced acetylcholine (Ach) level[5]. Chronic cellular damage from free radicals, excitotoxicity, nonenzymatic glycation of proteins, and other factors contributes to the loss of neurons and synapses that is associated with old age and aggravates the pathology of AD.

Neuro inflammation: There is evidence that inflammatory and immune mechanisms are involved in the pathogenesis of AD. Acute-phase proteins are elevated in serum and deposited in SPs, microglial cells, accumulate around SPs and complement components are present in SPs. APP is an acute phase protein which is released in brain tissue following trauma and other insults. The effects of neuro inflammation are mediated by activated microglial cells, which are a source of cytokines and a potent generator of free radicals.

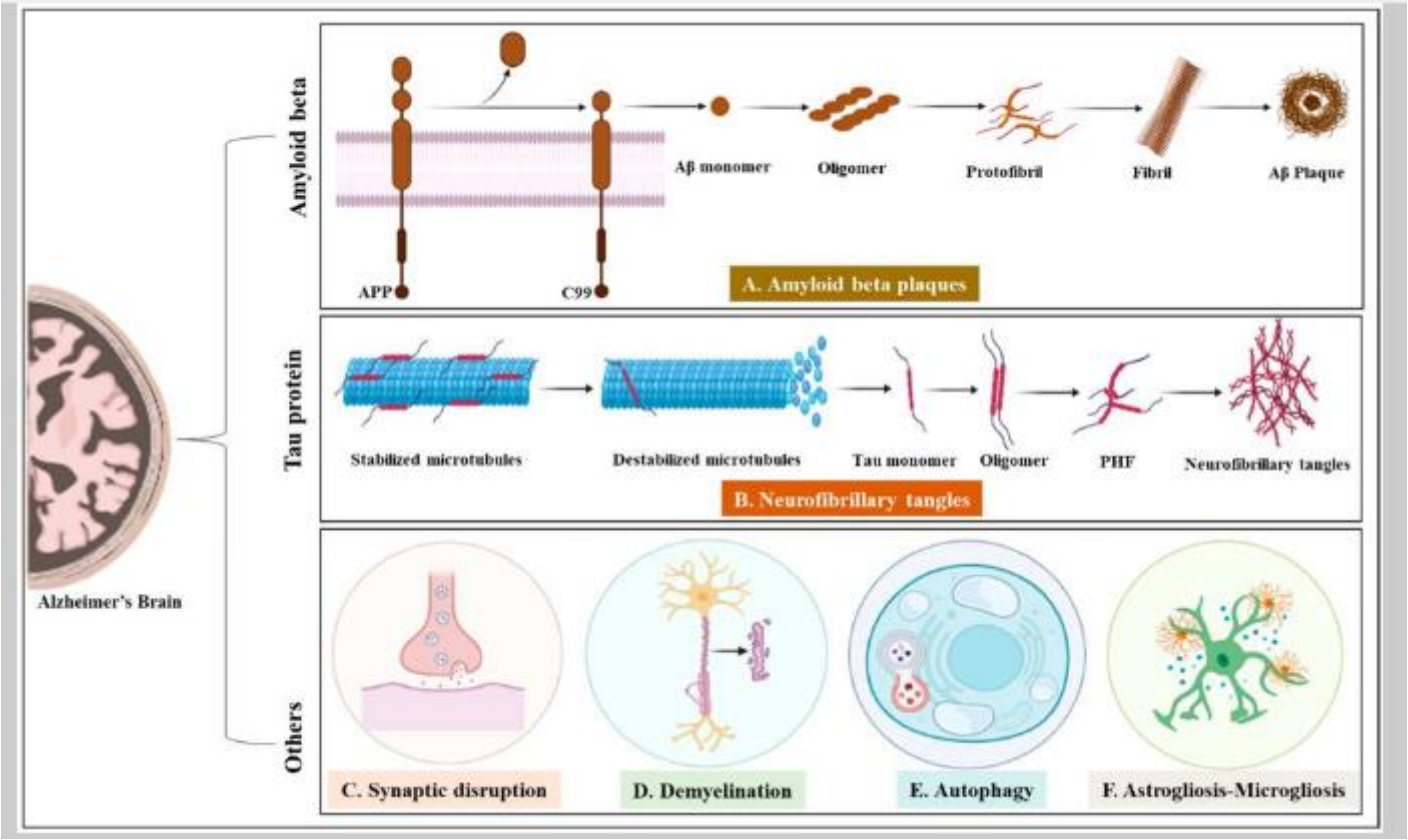

Figure 1: Pathophysiological changes in the CNS in AD (A) Formation of Aβ plaques. (B) Formation of NFT. (C) Synaptic disruption. (D) Demyelination. (E) Autophagy. (F) Astrogliosis–Microgliosis. (Created with BioRender.com accessed on 10 August 2023).[4]

Free radicals: Oxidative stress, compounding with advancing age, causes mitochondrial DNA mutations, mitochondrial dysfunction and more oxidative stress. This process is accelerated in AD by the action of A*β* (a mitochondrial poison and free radical generator) and activated microglia, also a source of free radicals.

Diabetes: Type 2 diabetes is a risk factor for AD. AD patients have low levels of insulin and insulin resistance in the brain. These changes impair energy metabolism in neurons and adversely affect signaling pathways dependent on insulin and its receptors. Furthermore, nonenzymatic glycation of proteins produces neurotoxic derivatives that aggravate oxidative damage.

Traumatic brain injury: Dementia and Parkinsonism develop sometimes in boxers, football players and other individuals who have had repeated cerebral concussions. This entity has been previously called dementia pugilistica (or the punch drunk syndrome) and was recently renamed Chronic Traumatic Encephalopathy (CTE)**.** The brain in CTE shows mainly NFTs. Diffuse and less frequently neuritic plaques are seen inconstantly.

Homocysteine: Increased levels of homocysteine (also a risk factor for stroke) and decreased dietary folate potentiate these neurotoxic effects. Homocysteine increases with advancing age and is elevated in persons with polymorphisms of 5,10-methylenetetrahydrofolate reductase (MTHFR), an important enzyme involved in folate metabolism. Such polymorphisms are very common. Elevated homocysteine and decreased folate are associated with increased free radicals, cytosolic calcium, glutamate excitotoxicity, apoptosis and decreased levels of ATP.

Old age: The fact that many people in their 80s and 90s are mentally intact indicates that dementia is not an inevitable accompaniment of old age. Nonetheless, statistics back up plain life experiences in showing that the main risk factor for AD is old age. The risk for developing AD in old age can be assessed partially based on the ApoE genotype. The contribution of general health and the environment is difficult to factor in and there may be other genetic risk factors that we don't know about. Possibly, whether a person with ApoE4/4 develops AD at 70 vs 75 years depends on general health and the environment. Stroke, CNS infections, traumatic brain injury, and any type of brain damage deplete structural and functional reserves and aggravate the dementia[6].

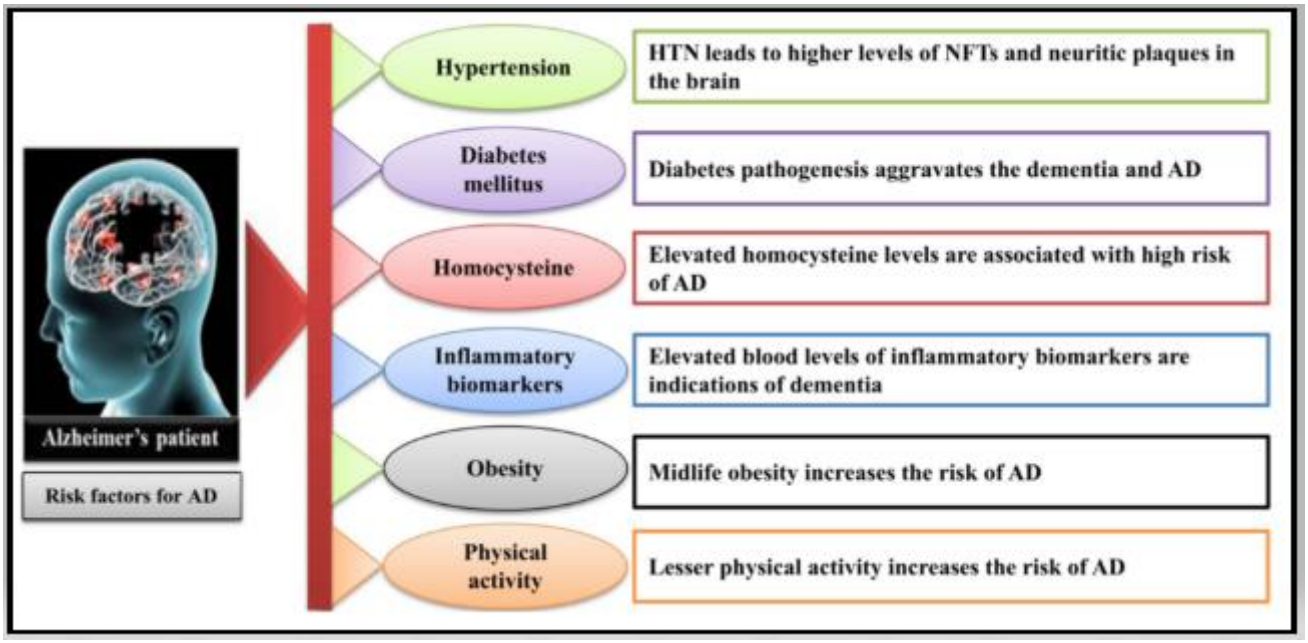

Figure 2: The life style and age related factors involved in the onset of AD. AD Alzheimer's disease, HTN Hypertension, NFT neurofibrillary tangles.

Pathophysiology: Early in the pathogenesis of AD, there is a progressive deposition of *β*-amyloid (*Aβ)*- peptide in the hippocampal and cerebral cortical regions. This deposition is associated with the presence of neurofibrillary tangles (NFTs) and senile plaques.

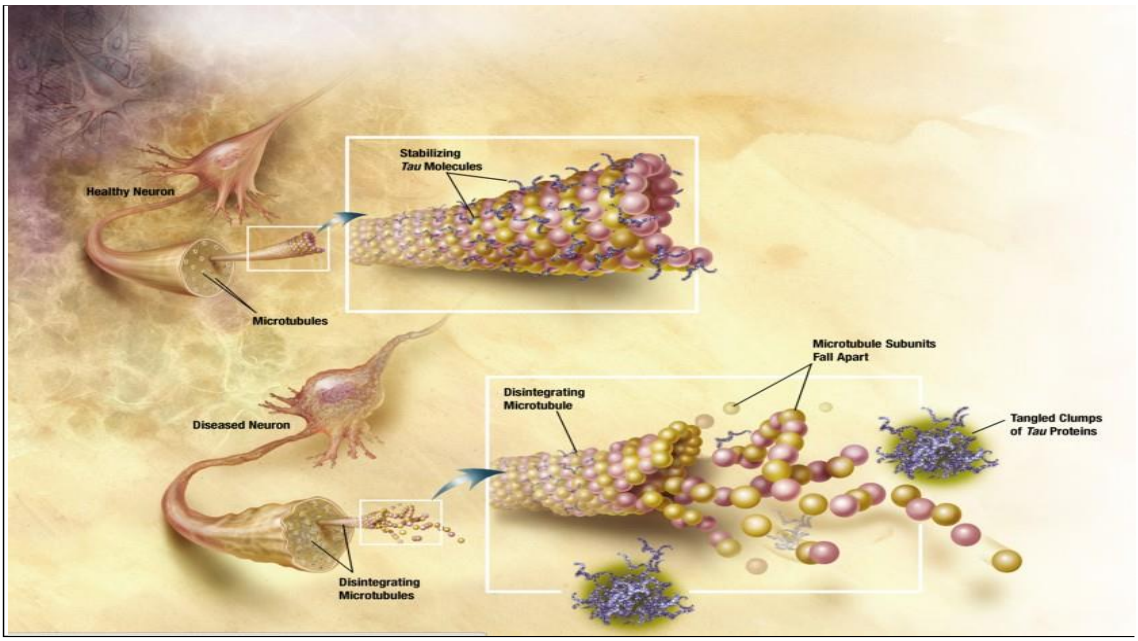

Figure 3: Diagram of how microtubules disintegrated with Alzheimer's disease[7]

Alzheimer's disease education and referral center, a service of the National Institute on Aging[7]. NFTs formed mainly by aggregates of hyperphosphorylated microtubular *Tau* proteins, whereas senile plaques are complex extracellular lesions in which the A*β*-containing core is surrounded by reactive microglia, fibrillary astrocytes, interleukins and dystrophic neuritis[8].

Role of BBB in the Pathogenesis of AD

The human CNS is a complex system that is well distinguished by two specialized barriers in the form of cerebrospinal fluid barrier. BBB plays a crucial role in the pathogenesis of AD. In AD, cerebrovascular dysfunction results in cognitive impairment and dementia, which may lead to cerebral amyloid angiopathy. It also mediates the accumulation of Aβ peptides in the brain. The BBB is important for the regulation of Aβ transport to brain via two primary receptors, namely, (1) receptor for advanced glycation end products (RAGE) and (2) the low density of lipoprotein receptor related protein 1 (LRP1). The faulty clearance of Aβ via the deregulated RAGE/LRP1 receptors, arterial dysfunction, and impaired angiogenesis may commence Aβ accumulation, neurovascular uncoupling, brain hypoperfusion, cerebrovascular regression, and neurovascular inflammation. Eventually, these events result in compromised BBB and subsequent neuronal and synaptic impairment. BBB: A LIMITING FACTOR IN DRUG DELIVERY TO BRAIN Blood–brain barrier plays a pivotal role in shuttling biomolecules in and out of the brain neuronal system. Therefore, understanding the structural and functional characteristics of BBB is essential for improving the

drug delivery to the brain. This protective unit factor helps to prevent shuttling of molecules between blood and brain composed of vascular endothelial cell layers bound back by tight junctions and other supportive structures. The endothelial cells are surrounded by a basement membrane covered by astrocyte end-feet and continuously monitored by surveying microglial cells. Cohesive domains, bound to endothelial cells, provide perseverance for the selective transport of small molecules across the BBB. To meet the requirements of proteins and peptides for brain homeostasis, a controlled intracellular transport occurs via transcytosis. Depending on the nature of the molecules (hydrophilic and hydrophobic), endothelial cells with the help of various special transporting proteins could facilitate the transport. To cure brain illness like AD, different nanocarriers have been reported in preclinical studies.

NOSE-TO-BRAIN DRUG DELIVERY AND LIMITATIONS

The delivery of drugs to the brain via the nasal route generally starts from the respiratory epithelium to the olfactory region with the help of the trigeminal nerve and olfactory nerve cells. This drug delivery route is supposed to transport the drug molecules to different parts of the brain including the frontal cortex, olfactory bulb, cerebrum, and brain stem. To deal with AD, the mechanism of drug transport into the brain can be classified in two ways, namely, intracellular drug transport and extracellular drug transport. Intracellular drug delivery is the intraneuronal route of drug transport. This route of transport is relatively slow and takes around 24 h to reach from the nasal cavity to brain cells. After entering the nasal cavity, exploiting the mechanism of endocytosis, the drugs could move to olfactory sensory neurons and peripheral trigeminal neurons via the olfactory and respiratory epithelium, respectively.

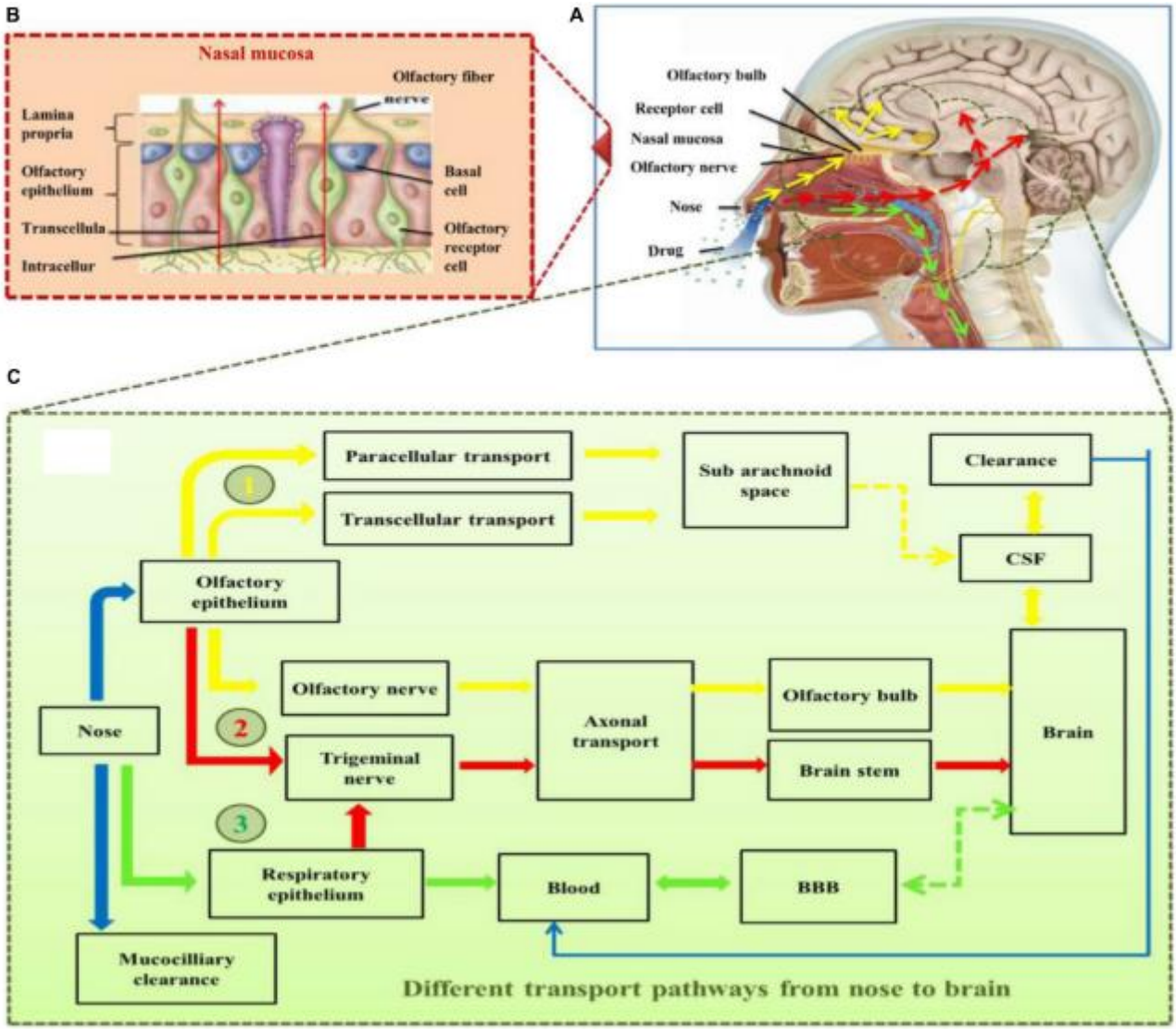

Figure 4: (A) Skull structure presenting major components of nose and brain involved in drug transport to the brain, (B) structural components of nasal mucosa, (C) the various pathways (highlighted in different colors; yellow, red, and green) for the delivery of drugs into the brain through intranasal route. Yellow arrows present the major direct pathway involving the olfactory nerve, red arrows present the pathway primarily involving the trigeminal nerve route, and green arrows illustrate the minor pathway involving blood–brain barrier (BBB) following the systemic absorption of the drug molecules through respiratory epithelium. BBB, blood–brain barrier; CSF, cerebrospinal fluid.[9]

Further from nerve cells, intracellular and transcellular transports mediate the movement of drug to different parts of the brain. The intracellular route delivers the drug to the olfactory lobe from the olfactory nerve and to the brain stem from trigeminal nerves. At the same time, the transcellular route provides the drug to the lamina propria, which further enters the brain through different ways. This type of transport facilitates the delivery of those drugs coated with lipophilic molecules that can adopt the passive diffusion or active transport/receptor-mediated transcytosis. Extracellular transport facilitates the transport of hydrophilic drug substances, various proteins and peptides. This is the sharp route of drug delivery from the nose to the brain and it is further divided into slow and fast extracellular transport. Extracellular transport of drug is the fastest route of drug delivery from the nose to the brain. In this route, drug molecules use the intercellular clefts in the olfactory and respiratory epithelium and extracellular transport along the olfactory and trigeminal neural pathway to reach the spinal fluid and brain. Once the drug reaches the lamina propria, there are different options including (i) getting into systemic circulation via being absorbed in olfactory blood vessels, (ii) it may enter nasal lymphatic vessels, (iii) or it may enter the cranial compartment associated with olfactory nerve bundles by extracellular diffusion. The challenges encountered in this route are mostly associated with the physicochemical properties of drugs, including molecular weight, lipophilicity, characteristics of the drug formulation, and the presence of specific receptors on the mentioned routes. The drug in the nasal route may be eliminated by mucociliary clearance or through CSF into blood. It is also reported that the surface charge, type, and concentration of the nanomedicine carrier also influence the drug delivery to the brain In other limitations, sometimes due to the nature of the NPs used, e.g., phospholipid complexes target inflammatory sites and the reticuloendothelial system by themselves. Some other functionalized NPs tend to adsorb an arbitrary biological entity and form a protein sheath, referred to as a "protein corona," which leads to the non-targeted interaction of drugs and also random deposits/accumulation of the carrier substance in biological systems. In order to achieve a sufficient therapeutic level in the target region of human brain, there has been a continuous struggle to improve the uptake of those drug-encapsulated nanocarriers and to explore the safest transport mechanisms after absorption. Various pathways for the delivery of therapeutic moieties from the nasal route to the brain are illustrated in Figure 4.

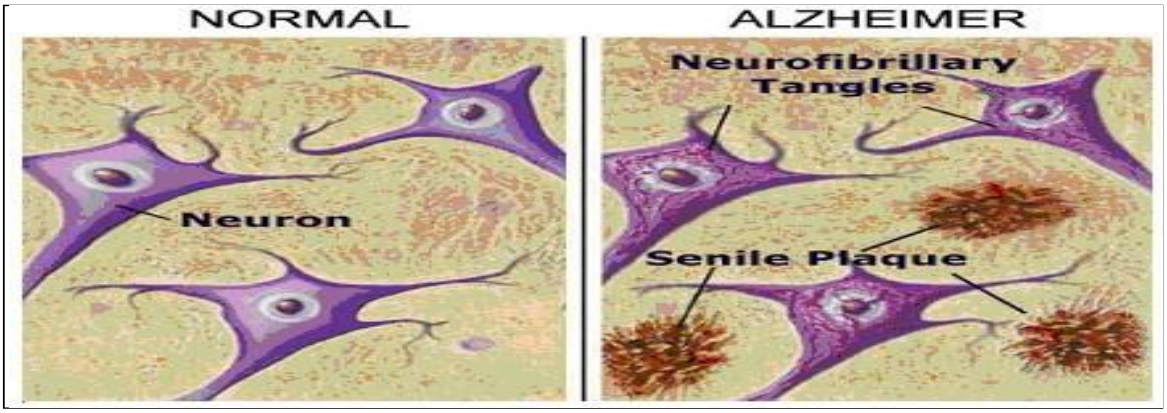

Figure 4: Degenerative changes in the brain of Alzheimer's disease.

The senile plaques deposited between the neurons consist mainly of the protein *β* amyloid. Neurofibrillary tangles deposited inside the neurons fabricated from *Tau* protein. Illustration from American Health Assistance Foundation[10]

Alzheimer's disease brain tissues are also characterized by neuro-inflammatory changes that, together with A*β* deposition and induction of glutathione depletion, might increase

the levels of reactive oxygen species (ROS) and account for vulnerability to oxidant attack[11, 12].

Beta amyloid: A*β* is a 36 to 43 amino acid peptide, which is part of a larger protein, the Amyloid Precursor Protein (APP). APP is a transmembrane protein, made by neurons and other brain cells. It is also found in extraneural tissues and is especially abundant in platelets. Its function is unknown. The A*β* amyloid residue includes part of the transmembrane domain of APP and is derived from cleavage of APP by the enzymes *β*-and *γ*-secretase. A*β* monomers and oligomers are further degraded by other enzymes. Defective clearance of A*β* from aberrant cleavage of APP and other mechanisms results in its accumulation. A*β* monomers polymerize initially into soluble oligomers and then into larger insoluble fragments such as A*β*42, which precipitate as amyloid fibrils.

Tau: Neurofibrillary degeneration is characterized by the deposition in the neuronal body and processes of insoluble polymers of over-phosphorylated microtubule associated protein Tau. Tau aggregates as pairs of filaments that are twisted around one another (paired helical filaments). These deposits interfere with cellular functions by displacing organelles. By distorting the spacing of microtubules, they impair the axonal transport thus affecting the nutrition of axon terminals and dendrites. No mutations of the Tau gene occur in AD. Abnormal Tau first appears in the entorhinal cortex, then in the hippocampus and at later stages in association cortex[6]

Diagnosis of AD

There is no single test that can show whether a person has Alzheimer's. While physicians can almost always determine if a person has dementia, it may be difficult to determine the exact cause. Diagnosing Alzheimer's requires careful medical evaluation, including:

- A thorough medical history
- Mental status testing
- A physical and neurological examination
- Tests (such as blood tests and brain imaging) to rule out other causes of dementia -like symptoms[13, 14].

Medication to treat AD

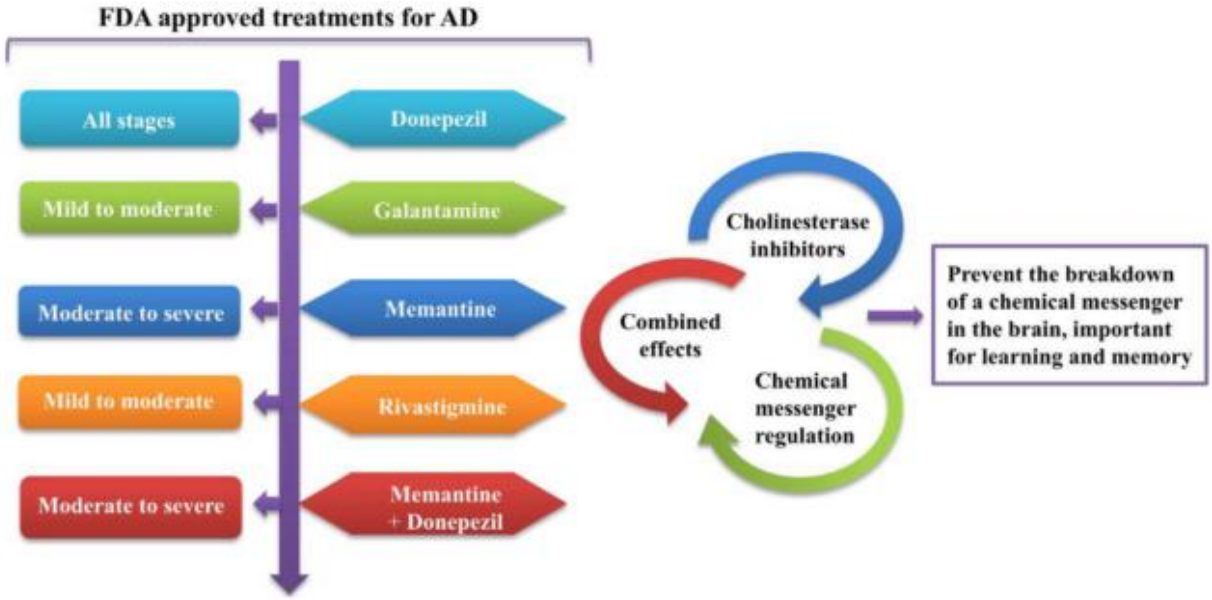

Figure 5: The functioning of currently FDA-approved drugs to treat the symptoms of AD. FDA, Food and Drug Administration; AD, Alzhiemer's disease [9]

Management of AD patient challenges both physicians and caregivers[15-17].

At present, two classes of medications approved to treat AD[18]:

- Cholinesterase inhibitors (ChEIs): Donepezil, Rivastigmine, Galantamine
- NMDA receptor antagonists: Memantine

Brief description about them is given below:

Cholinesterase inhibitors (ChEI):

Cholinesterase inhibitors slow down the degradation of acetylcholine in the synapticleft and compensate for its deficiency[19, 20].

Donepezil

It is also known as Aricept® (Pfizer, NY, USA). Donepezil is a reversible, noncompetitive and selective ChEI that produces long lasting inhibition of brain AchE without markedly affecting the peripheral AchE activity[21]. Donepezil was approved in 1996 in the US for the treatment of dementia of the Alzheimer's type and is available as 5 and 10 mg conventional immediate release tablets[22]. Donepezil prevents the breakdown of acetylcholine in the brain. Side effects associated with Donepezil are nausea, vomiting and diarrhea.

Rivastigmine

It is also known as Exelon® (Novartis, Switzerland). Rivastigmine is a dual inhibitor of both AchE and butyrylcholinesterase. It has been available since 1998 in the EU and was approved for use by the FDA in 2000 in the US for the treatment of mild to moderate AD[23]. Rivastigmine Tartrate is available as 1.5 mg (yellow), 3 mg (orange), 4.5 mg (red) and 6 mg (orange and red) capsules and as 2 mg/ml oral solution for conventional oral delivery[24]. Rivastigmine prevents the breakdown of ACh and butyrylcholinesterase in the brain. The side effects associated with Rivastigmine are nausea, vomiting, diarrhea, weight loss, loss of appetite and muscle weakness[25].

Galantamine

It is also known as Razadyne® (Ortho-McNeil Neurologics, Inc., Titusville, NJ, USA) marketed as Reminyl®. It is available as circular biconvex film coated immediate release tablets, which are available as 4 mg (off-white), 8 mg (pink) and 12 mg (orange-brown) coated tables[26]. It is approved by the FDA, but the first to come off- patent and become available in generic form[27]. It prevents the breakdown of ACh and stimulates nicotinic receptors to release more ACh in the brain. Side effects associated with Galantamine are nausea, vomiting, diarrhea, weight loss, loss of appetite[25].

NMDA receptor antagonists Memantine

It is also known as Namenda® (Forest Pharmaceuticals, Inc., St Louis, MO, USA). It is available as 5 and 10 mg film coated tablets and as 2 mg/ml oral solution for conventional delivery of Memantine hydrochloride. It was approved in October 2003 in the US for the treatment of moderate to severe stage of AD. Its safety and efficacy are supported by several large-scale, controlled clinical studies[28-30]. It blocks the toxic effects associated with excess glutamate and regulates glutamate activation. Side effects associated with Memantine are dizziness, headache, constipation and confusion[25].

Nanoparticulate drug delivery system

Nanotechnology and Nanoscience are widely seen as having a great potential to bring benefits to many areas of research and applications[31]. Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of 10^{-9} or one billionth. Nanotechnology focuses on formulating therapeutic agents in biocompatible nanocarriers, such as nanoparticles (NPs), nanocapsules, micellar systems and dendrimers. Moreover, one of the major advantages that nanotechnology offers is targeted drug delivery to the site of disease.

Over the past few decades, researchers have had considerable interest in developing biodegradable NPs as a drug delivery system (DDS). Moreover, they also exhibit a good potential for surface modification and functionalization with different ligands, provide excellent pharmacokinetic control and are suitable to encapsulate and deliver a plethora of therapeutic agents.[32,33]

Nanotechnology is enabling technology that deals with nano-

meter sized objects. It is expected that nanotechnology should be developed at several levels: materials, devices and systems. At present the nanomaterials level is the most advanced at present, both in scientific knowledge and in commercial applications. A decade ago, nanoparticles were studied because of their size-dependent physical and chemical properties.[34]

The major goal in designing nanoparticles as a delivery system are to control particle size, surface property and release of pharmacologically active agents in order to achieve the site specific action of the drug at the therapeutic optimum rate and dose regimen[35].

The advantages and disadvantages of using nanoparticles as a drug delivery system are as follows[36-39].

Advantages

- ✓ Increased and improved bioavailability
- ✓ Site specific drug delivery
- ✓ Sustained release of drug over long period of time
- ✓ Retention of dosage form in entire length of gastrointestinal tract
- ✓ Convenient to patient due to reduction in continuous dosing
- ✓ Higher carrier capacity
- ✓ Prolonged circulation time
- ✓ Stable in blood
- ✓ Acquiescent to small molecules, peptides, proteins or nucleic acids

Disadvantages

- ➢ Increase in cost of formulation
- ➢ May cause allergic reactions
- ➢ Over use of polyvinyl alcohol as a stabilizer may have toxic reactions

Delivering drugs to CNS is impaired by the presence of the BBB that represents the main obstacle for CNS drug development, many hydrophilic drugs and neuropeptides Etc. may have difficulty in crossing the BBB. It is important to consider not only the net delivery of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Many strategies have been developed to deliver the drug into brain by crossing the BBB: chemical delivery systems, magnetic drug targeting or drug carrier systems such as antibodies, liposomes or nanoparticles. Among those, nanoparticles have got a great concentration as the potential targeted drug delivery systems in the brain recently.[40]

Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment, must pass the BBB usually by nanoparticles drug delivery system, which is an advanced technology to deliver drug molecules into the brain. The main advantage of nanoparticles technology is that they masquerade the BBB restrictive features of the therapeutic drug molecule. These polymeric nanoparticles (NP) have been proposed as fascinating colloidal systems that allow slow drug release in brain and the improvement of therapeutic efficacy and reduction of toxicity of large variety of drugs. Due to their targeting ability they are very advantageous than other conventional drug delivery systems. Once the NP reaches the desired tissue, release of the drug may occur by desorption, diffusion through the NP matrix or polymer wall or NP erosion or combination of any or all mechanisms.[41]

These systems are attractive because the methods of preparation are generally simple and easy to scale-up. Due to their small size, nanoparticles penetrate into even small capillaries and are taken up within cells, allowing an efficient drug accumulation at the targeted sites in the body. The use of biodegradable materials for nanoparticles preparation, allows sustained drug release at the targeted site over a period of days or even weeks after injection.[42]

Some important DDS developed using nanotechnology principles are:[43]

- ✓ Nanoparticles
  - o Solid lipid nanoparticles
  - o Polymeric nanoparticles
- ✓ Nanosuspensions
- ✓ Nanoemulsions
- ✓ Nanocrystals

Nanoparticles:

The nanoparticles are the solid colloidal particulate systems with size ranging from 1to 1000 nm that are utilized as drug delivery system.[41]

Polymeric nanoparticles: Polymeric nanoparticles are used as potential drug delivery systems due to its target ability to a particular organ or tissue. Certain properties like hydrophobicity, lipophilicity, surface charge needs to be altered. So uptake of nanoparticles into cells increased by manipulating the use of polymers[44]. Nanoparticles generally made up of biocompatible and biodegradable polymers, which are obtained from either natural or synthetic source. The kinetics of drug release from nanoparticles depends on strength of hydrophobic and lipophilic interactions between the polymer, drug and polymer degradation rate.

Based on arrangement of drug and polymer matrix nanoparticles are classified into two types45:

Nanospheres: Drugs are either absorbed/entrapped inside the polymer matrix.

Nanocapsules: Drug present in the inner liquid core and external surface of nanoparticles are covered by the polymeric membrane

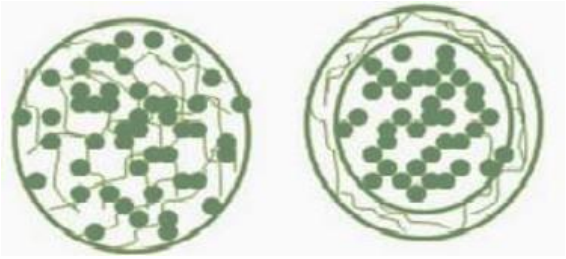

Figure 6: Schematic diagram of (A) Nanosphere, and (B) Nanocapsule[46]

Method of preparation of nanoparticles: [47]

- ✓ Precipitation technique
- ✓ High pressure homogenization
- ✓ Lipid emulsion/micro-emulsion template
- ✓ Melt emulsification method
- ✓ Milling techniques

Methods are described in detail as follow:

Precipitation technique: The drug is dissolved in an organic solvent and then the solution is mixed with a miscible anti-solvent for precipitation. In the water- solvent mixture the solubility is low & the drug precipitates. Precipitation has also been coupled with high shear processing. This is accomplished by combination of rapid precipitation and high pressure homogenization. Rapid addition of drug solution to an anti-solvent leads to sudden super-saturation of the mixed solution and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favoured at high super-saturation when the solubility of amorphous state is exceeded.

High pressure homogenization: In the high pressure homogenization method, the suspension of a drug & surfactant is forced under pressure through a nanosized aperture value of a high pressure homogenizer. The principle of this method is based on cavitation forcesof drug particles in the aqueous phase. These forces are sufficiently high to convert the drug microparticles into nanoparticles.

Lipid emulsion / micro-emulsion template: Lipid emulsion technique is applicable for drugs are soluble in either volatile organic solvents or partially water miscible solvents. An organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactant to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspensions, which is centrifuged and nanoparticles are separated, followed by redistribution in distilled water and lyophilization to get nanoparticles. Another way to produce nanoparticle is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase.

Milling technique: In this technique drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media and pearls are rotated at a very high shear rate.

Dry co-grinding: Recently, nanoparticles can be obtained dry co-grinding can be carried out easily and economically and can be conducted without organic solvents. It can reduce particles to the sub-micron levels and the stable amorphous solid can be obtained.

Solid lipid nanoparticles (SLN): Solid lipid nanoparticles are colloidal carriers are made up of solid hydrophobic core having monolayer of phospholipids coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics[48].

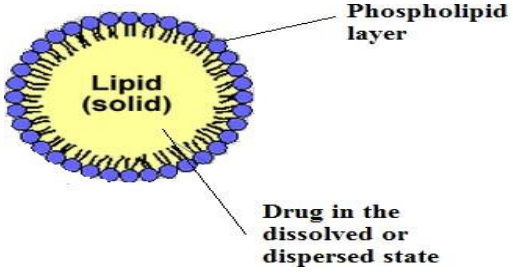

Figure 6: Structure of solid lipid nanoparticle[48]

SLNs are in the submicron size range of 50-1000 nm and composed of physiologically tolerated lipid components, which are in solid state at room temperature. They have many advantages as good biocompatibility, low toxicity. Lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable[49].

Advantages of SLN [50-53]

1. Small size and relatively narrow size distribution, which provide biologicalopportunities for site, targeting brain for enhanced penetration of drug into brain
2. Preparation of biodegradable physiological lipids, which decrease the danger ofacute and chronic toxicity and avoidance of organic solvent in production method
3. SLNs have better stability compared to liposomes
4. Enhances the bioavailability of bioactive and chemical production of labileincorporated compound
5. Easy to scale up and sterilize
6. Protection of chemically liable agents from degradation in the gut and sensitive molecules from outer environment
7. Much easier to manufacture than biopolymeric nanoparticles
8. Improves bioavailability of poorly water soluble molecules
9. It can be subjected to commercial sterilization procedure
10. No toxic metabolites are produced
11. Conventional emulsion manufacturing methods are applicable
12. No organic or other special solvent required
13. Surface modification can easily be accomplished and hence can be used for site specific drug delivery system

Disadvantages of SLN [54-55]

1. Limited drug loading capacity due to solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of lipid matrix
2. Drug expulsion during storage due to the formation of perfect crystal Particle growing, unpredictable gelation tendency
3. Unexpected dynamics of polymorphic transition
4. High water content of SLN dispersion (70-99.9%)
5. Adjustment of drug release profile

Method of preparation of solid lipid nanoparticles:

High pressure homogenization (HPH)

Hot homogenization

Cold homogenization

Solvent evaporation method/Solvent emulsification evaporation technique

Solvent diffusion method/Solvent emulsification-diffusion method

Supercritical fluid method

Microemulsion based method

Double emulsion method

Solvent injection technique

Spray drying method

Secondary production steps

Sterilization

Lyophilization

Characterization of nanoparticles:

Particle size and Zeta potential

Drug content and drug release

Electron microscopy

Atomic Force Microscopy (AFM)

Dynamic Light Scattering (DLS)

Differential Scanning Calorimetry (DSC)

Nuclear Magnetic Resonance (NMR)

Stability of SLN

Conclusion

Alzheimer's disease (AD) is indeed a complex and challenging condition, and the development of effective treatments is a critical area of research. The pathogenesis you described highlights the key role of β-amyloid (Aβ) peptide deposition and neurofibrillary tangles (NFTs) in the progression of the disease. Diagnosis is multifaceted, involving thorough medical evaluation and various tests to assess cognitive function and neurological status. The cholinesterase inhibitors and NMDA receptor antagonists reflects the current pharmacological approaches to managing AD symptoms, albeit with limited effectiveness in halting disease progression.

Nanoparticles hold promise as a delivery system for drugs targeting the central nervous system (CNS), including those for AD treatment. Their ability to control particle size, surface properties, and drug release kinetics can enhance drug delivery to specific brain regions while minimizing systemic side effects. Strategies such as nanoparticles offer potential avenues to overcome the blood-brain barrier (BBB) and deliver therapeutics totheir intended targets within the CNS.

Continued research in this area is crucial for developing more effective treatments that can slow or halt the progression of AD, ultimately improving the quality of life for those affected by this devastating disease.

Contribution of Authors

All authors contributed to the

Writing as well as critically reviewed and approved the final manuscript.

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Conflicts of Interest

The authors declares that there are no Conflicts of Interest

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