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Nanoparticles – a novel theranostic approach to treat alzheimer's disease

Abstract

The incidence of Alzheimer's disease (AD) is increasing day by day worldwide, which results in a poor quality of life. Early diagnosis and treatment of AD is necessary to suppress the progression of the disease. Conventional treatments have several limitations due to the protective blood-brain barrier. In this review, we described a nanoparticle-based approach to crossing the blood-brain barrier for AD detection and treatment. Nanoparticles encapsulate the anti-AD drug and are directed to the target tissues where controlled release of the drug takes place. There are various types of nanoparticles that are used to encapsulate drugs, including solid-based nanoparticles, liposomes, nanoemulsions, iron NPs, cerium NPs, selenium NPs, and gold NPs. In this review, we have described the use of different nanoparticles as nanomedicine. Nanoparticles are also coated with proteins and antibodies for efficient release of drugs. This review aims to provide clinical insights and the importance of nanotechnology in theranostics and describes how nanomedicine has revolutionized the drug delivery approach for AD treatment.

Keywords: alzheimer's disease, β-amyloid, aggregation, theranostics, nanomedicine

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Introduction

Alzheimer's Disease (AD) has been the most common type of dementia and is characterized by progressive neuronal degeneration due to β-amyloid plaque accumulation in the hippocampus.[1] Plaque formation in AD begins prior to the onset of its symptoms, thus making it difficult to understand its pathology.[2] There is an increasing prevalence of AD worldwide. It has been identified that about 50 million people in the world were diagnosed with AD in 2019, which increases the burden and greatly impacts the global economy. AD has become the 6th largest cause of death in the US and about 5.8 million people were affected by AD in 2020 (Figure 1).[3]

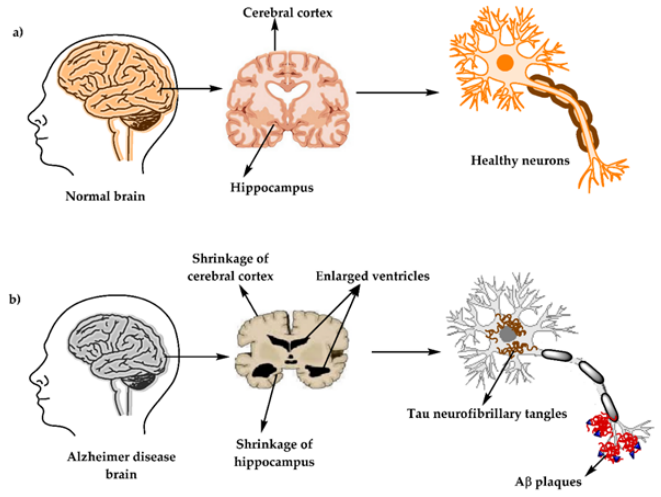

Figure 1 (a) Normal brain (b) Alzheimer brain.

AD can be defined as the loss of cognitive function, memory, and behavioural functions. It usually occurs in people of age 65 or older.[4] There is no proper treatment available for AD, but certain therapies are used to alleviate the symptoms. Clinical symptoms of AD vary depending upon the degree of illness. AD has been categorized into three stages depending upon the extent of cognitive decline: pre-symptomatic, moderate, and dementia. The primary and most common symptom of AD is short-term memory loss, which is followed by impaired abilities including thought, reasoning, decreased motivation, and impaired executive functioning. Several biological and environmental risk factors are associated with the development of AD.[4] Among the biological risk factors, trisomy 21 may be a reason for the early onset of AD. The APO E (Apo lipoprotein E) allele contributes to AD by increasing the formation of amyloid plaques. Other risk factors include aging, depression, smoking, cerebrovascular diseases, head injury, and increased levels of homocysteine (Figure 2).[5]

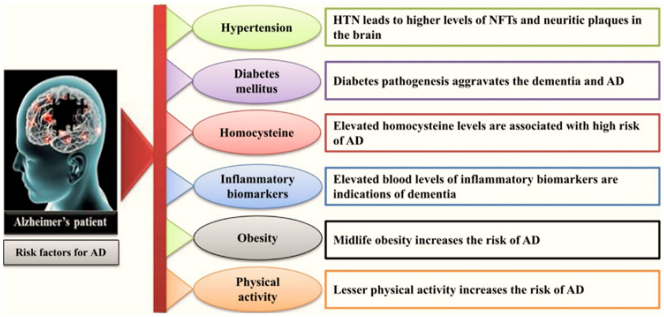

Figure 2 Risk factors for AD.

There are several difficulties to coping with the pathophysiology of AD. The medications to treat the cognitive decline in AD are mainly administered through the nose and based on enzyme regulation and neurotransmitter regulation.[6] However, these medicines have failed due to their pharmacodynamics and pharmacokinetic properties, including instability, reduced absorption in neurons, and cytotoxicity.[7] To deal with these problems, the use of nanoparticles (NPs) is a promising strategy to treat neurodegenerative diseases like AD and dementia. NPs have the capacity to cross the blood-brain barrier and have unique physicochemical properties that make them an ideal candidate to treat AD.[8] Targeted drug delivery using NPs can enhance the pharmacokinetics and pharmacodynamics of a drug and decrease its toxicity.[9] The main advantage of using NPs AD management is the controlled delivery of medicines at specific sites.[10] Nanoparticles have achieved considerable breakthroughs in a variety of fields, including medical, optical, and biological/chemical detection.

AD and blood brain barrier

The human Central Nervous System (CNS) is a complicated system differentiated by two distinct barriers, known as the cerebrospinal fluid barrier (CSFB) and the blood-brain barrier (BBB).[11] The blood-brain barrier is critical in the pathophysiology of Alzheimer's disease. Cerebrovascular malfunction in Alzheimer's disease causes cognitive decline and dementia, which can progress to brain amyloid angiopathy. It also plays a role in the deposition of Aβ peptides in CNS. The blood-brain barrier regulates Aβ transit to the brain through two major receptors: 1) LRP1 (low-density lipoprotein receptor related protein 1) RAGE (receptor for advanced glycation end products) is a receptor for advanced glycation end products. Poor Aβ peptide elimination due to LRP1/RAGE receptor dysregulation may result in Aβ accumulation, resulting in a weakened blood-brain barrier and neuronal damage.[12]

Importance of the blood-brain barrier in drug delivery

The blood-brain barrier (BBB) is critical in the transportation of biomolecules in the CNS. Therefore, it is essential to understand the functional and structural properties of the BBB for the efficient transport of drugs in CNS. This protective unit assists in the prevention of molecular shuttling between the brain and the blood, which is made of endothelial cells held back by strong connections and other supporting features.[13] Endothelial cells are bordered by a basal layer are constantly checked by microglial cells that examine that area. Cohesive domains, which are attached to endothelial cells, allow for selective transit of tiny molecules across the BBB. Several unique carrier proteins along with the assistance of endothelial cells, may be able to promote transfer based on the nature of compounds (hydrophobic or hydrophilic). Various nanocarriers have been described in preclinical investigations to treat brain disorders like Alzheimer's disease. These nanocarriers encapsulate anti-AD drugs as cargo and transport them across the BBB (Figure 3).[14]

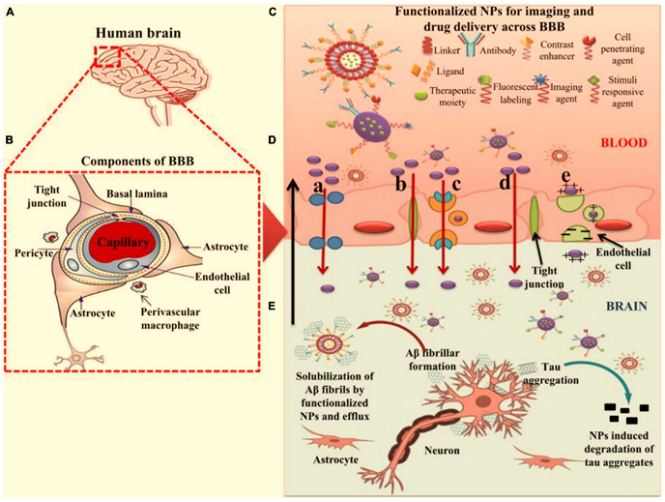

Figure 3 Role of BBB in drug delivery.

Nanoparticles-a new drug delivery strategy through BBB

Small-sized nanoparticles (NPs) have been used to treat brain disorders like AD and brain tumours for the effective delivery of FDA-approved, commercially available drugs. These nanoparticles containing medicines are known as nanomedicines. Currently, medicines for therapy of AD can only ameliorate clinical symptoms rather than eradicate the disease.[15] NP-functionalized nanomedicine is thought to be the most appropriate strategy for transporting the prescribed medications to the impaired region of the brain tissues.[15] Nanoparticles have a variety of special features that enable them to transport anti-AD medicines to particular sites in the CNS. Nanoparticle-based drugs have the benefits of decreased size and enhanced biocompatibility, which allow therapeutic compounds to be easily transported into the brain.[16] Nanomedicines are tiny and may readily contact receptors and chemicals on the surface of the cell as well as within the cell. NP-functionalized nanomedicines possess central core features that enable drug packaging or conjugation as well as safety and sustained blood flow. Nanoparticles are customized to targeted cells or even internal compartments i.e. Aβ accumulation in the cells, enabling the medicine to be transferred directly to the diseased location at a predefined dose. At the same time, nanocapsules can reduce dosage and frequency while improving patient adherence.[17] Irrespective of some clinical problems, nanomedicines are beneficial in terms of stability, biodegradability, biocompatibility, safety, prevention from degradation enzymes, bioavailability, and sustained release of drugs to treat AD.

Nanomedicines in the management of AD

Nanoparticles have extensive applications in treatment and diagnosis of AD. It is explained below how nanotechnology-based drug transport systems are involved in theranostic (therapy + diagnostics) of AD.

Liquid-based nanoparticles

Researchers have revealed that lipid-based nano-capsules are extremely important for use in drug transport systems to treat CNS disorders like Alzheimer's. Lipid nanoparticles offer an extraordinary capability for transporting anti-AD medicines via the nose to treat AD Figure 4.

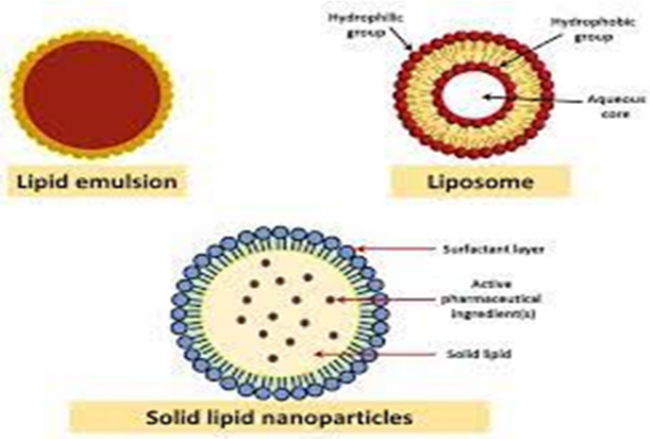

Figure 4 Liquid-based NPs.

Solid-lipid nanoparticles

In AD, solid lipid nanoparticles are thought to be effective transporters of a-bisabolol. The mixture resulted in a considerable inhibition of amyloid accumulation.[18] A new strategy for inducing the expression of transporters of breast cancer resistance protein and p-glycoprotein on endothelial cells of the brain was developed recently by targeting MC11 ligands. Transferrin-functionalized lipid nanoparticles may stimulate the production of these proteins, which can be considered as a viable method for Alzheimer's disease treatment.[19] The composition of solid lipid NPs filled with donepezil can improve drug transport to the brain via the nose in both in vitro and in vivo

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investigations.[20] Another study found that the liquid emulsification diffusion approach may be used to synthesize solid lipid NPs and donepezil formulations.[21] In comparison to other preparations, the outcome shows a significant improvement in therapeutic potential. Curcumin-loaded lipid-core nano-emulsions were recently created and successfully tested.[22] Curcumin nano-emulsions demonstrated strong neuroprotective benefits against Aβ1-42-induced cognitive and neurochemical alterations in an Alzheimer's disease mouse model. Likewise, Sdegh Malvajerd et al.,[23] reported that both nanostructured lipid vehicles and solid lipid nanoparticles packed with curcumin had strong neuroprotective benefits in the management of AD, with increased curcumin availability to the brain.

Liposomes-based NPs

The nanoparticle vesicles liposomes are amphiphilic and self-assembling, and they have been widely exploited as nanomedicines to transport medicines to cerebral tissues.[24] Liposomes may be easily functionalized and chemically modified with a variety of polyether, multifunctional proteins, and CPPs (cell-penetrating peptides) that help in the target-specific delivery of drugs through the BBB.[25] Curcumin-filled liposomes have been shown to greatly improve drug transport to the CNS via matching ligands on BBB cells. Apolipoprotein E (ApoE2) in brain tissues was modified with a modified surface comprising CPPs and mannose ligand. The findings suggest that functionalized liposomes are effective and safe in delivering high concentrations of genes to specific tissues in Alzheimer's disease treatment.[26]

Nanoemulsions

Nanoemulsion preparations improve the efficacy of anti-Alzheimer's drugs while also tailoring them to specific brain regions.[27] Nano-emulsion was employed to incorporate memantime through nose to circumvent the blood brain barrier in AD treatment. In vitro and in vivo studies showed that emulsion has potential benefits against AD pathology.[28] Naringerin nanoemulsion is being developed further in order to increase clinical effectiveness. The findings suggested that naringerin nanoemulsions might be a promising way to overcome Aβ toxicity and amyloid accumulation.[29]

Cubosome-based NPs

Cubosomes are lipid-based NPs with potential therapeutic applications for drug transport the CNS.[30] Patil et al.,[31] found that dopenzil-HCL infusion through cubosomes nasal gel can be regarded as potential carrier for transport of medication to treat impaired regions of CNS.

Metallic nanoparticles

The utilization of metallic nanoparticles in nanotechnology-based treatments for AD is regarded as an appropriate research topic for controlled medicine transport across the BBB. Metallic NPs have considerable limits because of the use of chemical procedures in their production, although several metallic nanoparticles, including selenium, cerium, iron, and gold, are believed to have strong anti-AD effects. Nowadays, scientists are focusing on using green chemistry-based techniques to develop physiologically friendly NPs.

Selenium nanoparticles

Reducing ROS levels in the brain is a key treatment strategy for Alzheimer's disease. Many trace metals, including sodium selenite (IV), sodium selenite (VI) and selenium (II) are strong inhibitors of ROS. Selenium-and selenite-containing NPs play a role in decreasing oxidative stress and preventing cell toxicity since they are key nutrients in the human body and have biological applications of selenium nano-emulsion. As a result, they can be employed in the treatment of neurological disorders such as Alzheimer's.[32] It has been discovered that altered selenium NPs containing sialic acid may traverse the BBB and suppress Aβ aggregation after exposure.[33]

Cerium nanoparticles

In an Alzheimer's disease patient, cerium oxide nanoparticles may preserve crucial brain function from elevated ROS levels. CeONPs have been shown to have no adverse effects and to be highly effective in the management of Alzheimer's disease.[34] The efficacy of ceria therapy for Alzheimer's disease can be linked to increased absorption through the BBB and no undesired build-up in other biological locations. Kwon et al.,[35] used Ceria NPs conjugated with tri-phenyl-phosphonium (TPP) concentrate in mitochondria and reduce neuronal mortality in a preclinical Alzheimer's disease mouse model. Another analysis revealed that FeO3/CeOx@PEG2,000 NPs may efficiently scavenge radicals and reduce oxidative stress.[36]

Gold nanoparticles

Gold nanoparticles serve critical functions in the transfer of drugs over the BBB to the CNS for the management of neurological diseases.[37] Several AuNP preparations are utilized for therapeutic and diagnostic purposes in the treatment of AD. Au NPs stabilized by D-glutathione may cross the blood brain barrier after intravenous infusion and demonstrate robust inhibitory activity against Aβ42 accumulation with no cytotoxicity in the AD mouse mode.[38] Recent study suggests that delivering maize tetrapeptide-anchored gold NPs can improve central cholinergic system function and reduce acetylcholinesterase activities, meaning that a novel tetrapeptide can be used as a neuroprotective therapy to combat AD.[39] Furthermore, research has revealed that treating AD rats with gold NPs greatly improved their symptoms by lowering neuroinflammation and modifying mitochondrial activity.[40]

Iron nanoparticles

FeO (Iron oxide) nanoparticles (NPs) have been employed in biological research. It has been explored if ultrasmall superparamagnetic FeO-NPs in combination with phenothiazine-based near-infrared (NIR) fluorescent dye can function as therapeutic drugs in the management of AD.[41] The nanoparticles can provide imaging of Aβ plaques by MRI and NIR fluorescenceand inhibit their aggregate in the brains of Alzheimer's disease mice.[42] Furthermore, protein-capped (PC) cadmium NPs and PC-Fe3O4 NPs can operate as strong tau accumulation suppressors in AD cells, suggesting a unique technique for developing anti-tau aggregate medicines for AD patients.[43]

Compositions for nanomedicine-theranostics

Au nanomedicne

The strategy implicated in the treatment of Aβ plaques using gold NPs (AuNPs) is like the molecular mechanism in the therapy of cancer cells with metallic NPs. The findings of molecular dynamics, time course simulation analysis and system biology system biology, and time course simulation analysis support and corroborate AuNPs' function to suppress Aβ accumulation in CNS.[44] AuNPs have been proved effective in identifying Alzheimer's disease, whether used alone or in combination with other chemicals. AuNP exposure helps alleviate neurological damage in the AD model due to its anti-inflammatory and antioxidant properties.[45] AuNPs use biosensor

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techniques to diagnose Alzheimer's disease pathology. AuNPs, for example, are being employed to detect tau proteins in the development of electrochemical immunosensors.[46] Additionally, chiral recognition of stable AuNPs has been discovered to improve their capacity to inhibit Aβ accumulation.[38]

Protein-coated nanoparticles

In biomedicine, the use of protein-coated NPs in multimodal therapeutic techniques is critical in the management of Alzheimer 's disease. Serum albumin (SA)-NP preparation has been demonstrated to improve the R-flurbiprofen efficacy in reduction of Aβ peptide cytotoxicity in CNS.[47] SA-NPs, such as R-flurbiprofen, are employed in the transportation of tacrine and can maintain bioavailability while causing little toxicity in liver.[48] Furthermore, nanoparticles in combination with sialic acid and BSA have been used to detect Aβ development at initial stage. Additionally, supplied NPs (protein-based) enhances the images of Aβ plaques, thereby acting as contrast agents.[49]

Antibody-coated nanoparticles

Administering immunotherapy dosages against amyloid aggregates to treat Alzheimer's disease has major side effects i.e., meningoencephalitis.[50] Utilization of NPs covered with antibodies against specific target proteins is best for reduction of adverse immunotherapy effects and detection of protein accumulations in brain cells.[51] Secondary ion mass spectrometry is used to image AD-associated proteins in the brain using an antibody coated with metal oxide NPs. Another research found that multifunctional FeO NPs coupled with scFv antibody specific to Aβ oligomer and receptor activator (class Aβ scavenger) had screening capability for Alzheimer's disease.[52] Abs-coated PEG NPs have been used to breakdown Aβ-42 and may successfully minimize neurotoxicity caused by Aβ fibrils in the Alzheimer's disease brain.[53,54]

Conclusion

Given the eventual aims of nanoparticles, there is a significant progress in the diagnosis and treatment of Alzheimer's disease. Nanomedicines have customized and altered both treatment and diagnosis techniques for Alzheimer's disease. For the bright future of nanotechnology employed in Alzheimer's disease, we propose revising present techniques to account for the overlooked elements at the nano-bio junction in order to reduce the risk of result misunderstanding. Multifunctional nanoparticles can also be used to regulate tau activation, inflammatory response, mitochondrial function and oxidative stress. Furthermore, challenges in producing reliable NPs on a big scale must be addressed.

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Conflict of interest

The authors declare that there is no Conflict of interest.

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