NL Neurology Letters

Review Article

https://doi.org/10.52547/nl.1.2.64

Role of Biomaterials in treatment of Alzheimer's disease: A literature review

Elham Ramezannezhad

School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Currently, five medications have been approved by the FDA to treat Alzheimer's disease (AD); Donepezil, which is used at all stages of AD, galantamine, and rivastigmine for mild to moderate stages, and Memantine and a combination of Memantine and donepezil for moderate to severe stages. The ability of these drugs to cross the blood-brain barrier (BBB) determines their exact efficacy. Numerous biomaterials were introduced as a vector for drug agents and increased bioavailability. In this review, we summarized several biomaterials which were used in the treatment of AD.

Keywords: Alzheimer's disease, biomaterials, nanocarriers, nanoparticles

Correspondence to Elham Ramezannezhad, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Email: eramezannejad@gmail.com

Published online 30 December 2022

Cite this article as: Ramezannezhad, E. Role of Biomaterials in treatment of Alzheimer's disease: A literature review. Neurology Letters, 2022; 1(2): 64-68. doi: 10.52547/nl.1.2.64.

Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia and is the sixth leading cause of death worldwide (1). AD is expected to affect 1 in every 85 people by 2050. (2). Memory loss, disorientation of time and place, dramatic personality changes, and poor judgment are all signs of AD that worsen as the disease progresses (3). Amyloidopathy, which refers to the accumulation of amyloid beta (Aβ) protein in the brain, is one of the most well-known theories behind the pathogenesis of AD. Amyloid precursor protein (APP) is a transmembrane protein found in the CNS that is cleaved by γ- and α-secretase enzymes, resulting in the formation of Aβ monomers with 39–43 residues. Aβ1–42 is the most toxic type, resulting in a high potential for aggregation owing to its high hydrophobicity. Over time, toxic Aβ oligomers, fibrils, and plaques are developed from Aβ monomers and accumulate in the cortical and hippocampal areas (4). On the other hand, the role of tauopathy in AD pathology has received considerable attention since Aβ immunotherapy failed in several clinical trials (5). Tau is a microtubule-associated protein (MAP) whose functions are thought to be regulated by phosphorylation. Phosphorylated tau (P-tau) dissociates from microtubules and forms neurofibrillary tangles (NFTs), which disrupt synaptic transmission and inevitably lead to neuronal cell death (6). The impairment of the cholinergic system is also evident in AD patients and acetylcholine production is diminished due to the loss of cholinergic neurons and enzymes (7). Both A plaques and NFTs elicit immune responses, as well as microglia activation and inflammatory cytokine production. This inflammatory environment, along with oxidative stress and reactive oxygen species (ROS), causes neuronal death in a variety of brain areas (8). Currently, five medications have been approved by the FDA to treat AD; Donepezil, which is used at all stages of AD, galantamine, and rivastigmine for mild to moderate stages, and Memantine and a combination of Memantine and donepezil for moderate to severe stages. The ability of these drugs to cross the BBB determines their exact efficacy.

Although new treatments try to alleviate AD symptoms, replacing the lost cells can yield promising outcomes. Since transferring stem cells to the brain without a scaffold exposes them to a hostile environment, some peptides that could self-assemble into nanofibers and serve as scaffolds for neural stem

cells have emerged (9). Self-assemble peptides were developed to improve the cell-supporting properties of the previous self-assemble peptides, such as RADA16, which was composed of the amino acids Arg, Ala, Asp, and Ala and then modified with a laminin-derived peptide sequence. These materials decreased the apoptosis rate, increased neurotrophic peptides and anti-inflammatory cytokines, and rescued neural cells (10).

Polymeric nanoparticles

Polymeric nanoparticles are auspicious candidates for drug delivery due to their low toxicity and high drug-loading capacity. polymeric nanoparticles include poly (lactic-co-glycolic acid) (PLGA), Poly (lactic acid) (PLA), poly (butyl cyanoacrylate) (PBCA), chitosan, poly (glycolic acid) (PGA), poly (caprolactone) (PCL), and gelatin (9, 11).

PLGA is the most common nanomaterial in drug delivery for AD. Memantine is an approved treatment for AD, although it has not yet been proven to be completely effective. Sánchez et al. loaded memantine in PLGA, surface-coated with polyethylene glycol (PEG) to target the BBB and showed a decrease in Aβ plaque burden and improvement in memory impairment in transgenic APPswe/PS1dE9 mice in comparison to free drug administrated mice (12). Curcumin is a herbal polyphenol with anti-inflammatory and metal chelating; however, it has a low water solubility, a high clearance, and limited access to the BBB (13). Curcumin disaggregates Aβ plaques and attenuates hyperphosphorylation of tau protein but its low bioavailability makes it ineffective for therapeutic purposes (14). To compensate for curcumin's limited capacity to cross the BBB, Barbara et al. loaded it into PLGA nanoparticles. This resulted in a reduction in Aβ aggregates in vitro cultured hippocampal neuronal cells (15). In another study, Huang et al. designed a novel PLGA-nanoparticle by loading Aβ generation inhibitor S1 (PQVGHL peptide) and curcumin into a PLGA nanoparticle and conjugating it with a brain-targeting peptide CRT (cyclic CRTIGPSVC peptide). In transgenic AD mice, this PLGA nanoparticle decreased Aβ level and improved spatial memory and cognition while lowering inflammatory cytokines (16). Furthermore, PLGA can be combined with other materials to increase bioavailability. In this regard, Kuo et al. developed a lipid-coated polymeric nanoparticle consisting of polyacrylamide (PAAM)-cardiolipin (CL)-(PLGA) grafted with a monoclonal antibody to improve permeability and deliver rosmarinic acid and curcumin to the brain. This delivery method significantly enhanced the survival of the Aβ insulted cells (17). The etiology of AD is linked to the interaction between accumulated Aβ and excess metal iron. Quercetin is a natural product with properties essential for permeating the BBB. Sun et al. developed PLGA-functionalized quercetin (PLGA@QT) NP that inhibited the Zn2+-Aβ42 system neurotoxicity and ameliorated the memory function (18).

Another nanoparticle being investigated as a drug delivery mechanism is Poly (lactic acid) (PLA). To improve target binding in the brain, a PEGylated-(PLA) polymer was designed and conjugated with two targeting peptides (TGA and QSH). TGA binds to the BBB ligands and QSH has a good affinity with Aβ1-42. These nanoparticles achieved a precisely targeted delivery in transgenic AD mice models (19).

In the treatment of AD, growth factor-loaded nanoparticles are also being considered. PBCA has been used to deliver nerve growth factors (NGF). An increase in memory functions was observed after intravenous injection of NGF-loaded PBCA into an amnesic-induced mouse (20).

Chitosan is a biocompatible, low-toxic, and non-immunogenic material. Its mucoadhesive properties enable chitosan-based nanoparticles to penetrate the mucous membrane more effectively (21). As previously mentioned, rivastigmine is an FDA-approved anticholinesterase inhibitor with gastrointestinal side effects. These side effects are avoided when rivastigmine is administered through transdermal patches, but the drug's effectiveness is hampered due to its low diffusion (22).

The use of polysorbate-80 coated chitosan nanoparticles to encapsulate rivastigmine decreases adverse effects, increases the mean tolerated dose, and improves safety (23). Moreover, chitosan can be applied for nonpharmaceutical drug delivery. Curcumin-loaded nanoparticles conjugated with chitosan are suggested to enhance the bioavailability and macrophage phagocytosis of Aβ1-42 (24, 25).

Magnetic nanoparticles

Abnormal homeostasis of metal ions will hasten the progression of AD. The most important elements in this process are Fe, Zn, and Cu. Iron chelators have been conjugated into different nanoparticles including polystyrene and lipid nanoparticles (26).

Magnetic nanoparticles can be used as diagnostic probes in neurodegenerative disorders such as AD. Amyloid plaques can be identified in MRI images using iron oxide nanoparticles modified with protein motifs for biocompatibility and solubility (27). In a study by Fernández et al., magnetic nanoparticles were conjugated with anti-ferritin antibodies and transferred to transgenic AD mice which helped to recognize ferritin-accumulated brain regions, especially the subiculum and hippocampus (28). Likewise, magnetic nanoparticles have the potential to be used as a medication in AD treatment. In contrast to the native osmotin-treated mice, Faiz et al. loaded osmotin onto Dextran coated Fe3O4 magnetic nanoparticles and transmitted it to the brain of Aβ1–42-treated mice under functionalized magnetic field guidance, resulting in reduced Aβ accumulation, p-tau level, and synaptic deficits (29). Administration of gold nanoparticles preceded by exposure to a weak microwave field can help to dissolve Aβ fibrils and mitigate AD progression (30). Furthermore, Au nanoparticles combined with polyoxometalate have been shown to inhibit Aβ aggregation and Aβ fiber association (31). Aβ plaque can be probed with gold nanoparticles, which can aid in the diagnosis of AD. As such, the use of four fluorescent nanoparticles in conjunction with fluorescent intensity analysis of biological samples may be used to distinguish AD-specific proteins (32).

Liposomes

Liposomes are promising drug delivery systems that can cross the BBB due to their ability to combine with biological membranes. Liposomes are biodegradable materials with a PEG coating that can extend their circulation half-life (9). They can be surface engineered with anti-Aβ antibodies or deliver natural substances such as curcumin and quercetin, growth factors like brain-derived neurotrophic factors (BDNF), or therapeutic drugs including rivastigmine (33, 34). Quercetin encapsulation in liposomes grafted with lactoferrin and bradykinin analog has improved their ability to pass the BBB (35). Serotonin modulators can interact with serotonin receptors on brain microvessel endothelium and may modulate brain activities in AD, besides, apolipoprotein E can assist in crossing the BBB via low-density apolipoprotein receptors. Aβ targeting liposomes, surface coated with serotonin modulators and apolipoprotein E, delivering NGF simultaneously, elevated NGF permeation through BBB, decreased secretion of acetylcholine esterase, and preserved hippocampal serotoninergic neurons (36).

Micelles

Micelles can operate as a drug delivery system. Curcumin-loaded polymeric nanomicelles have been shown to inhibit amyloidogenesis through the glycation process of amyloid fibril synthesis (37). Even in the early stages of AD, mitochondrial dysfunction plays a crucial role in pathogenesis. As a result, delivering antioxidants to the mitochondria of impaired neurons can help to alleviate the progression of the disease. Yang et al. used neural cell adhesion molecules and triphenylphosphonium for mitochondrial targeting (CT-NM) to design a neural-mitochondrial targeted micelle, which was then loaded with resveratrol. CT-NM improved cognitive performance and attenuated Aβ deposition in transgenic AD mice (38). In another study, micelles were engineered to be able to accumulate in disease areas of the brain and exert ROS scavenging and Aβ inhibiting effects. To modulate the AD microenvironment in the brain, these micelles target microglia, and neurons in a sequential manner (39).

Dendrimers

Dendrimers are symmetric nano-sized molecules with a variety of properties, including polyvalency, low cytotoxicity, self-assembly, and solubility, which qualify them for medical purposes (40). Dendrimers are drug-delivery devices as well as therapeutic agents. Tacrine is an anticholinesterase activity that causes hepatotoxicity. Tacrine was co-administered with PAMAM dendrimers as a drug delivery mechanism, which reduced hepatotoxicity without interfering with its anticholinesterase activity (41). Another form of dendrimer that can reduce the cytotoxicity of intermediate metabolites during the Aβ aggregation process is cationic phosphorus dendrimers (CPD) (42). CPD can also inhibit acetylcholine esterase activity and decrease the secretion of TNF-α (43). Ester et al. developed dendrimers with a maltose histidine coating to enhance biocompatibility and ability to cross the BBB and demonstrated their effectiveness in preventing AD through synaptic protection (44).

Conclusion

Using the unique features of biomaterials, there were successful target-specific therapies. However, the main limitation is the lack of proper treatment for AD. The use of biomaterials offers a great opportunity for feature drug agents to reach maximum efficacy in AD patients.

Deceleration

Funding

We do not have any financial support for this study.

Conflict of interest

The author declares no conflict of interest regarding the publication of this paper.

Ethical approval

Since the data in this paper were obtained from the ADNI database (adni.loni.usc.edu), it does not include any research involving human or animal subjects.

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

References

1. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):88-106.
2. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007;3(3):186-91.
3. Neugroschl J, Wang S. Alzheimer's disease: diagnosis and treatment across the spectrum of disease severity. Mt Sinai J Med. 2011;78(4):596-612.
4. Pourhamzeh M, Joghataei MT, Mehrabi S, Ahadi R, Hojjati SMM, Fazli N, et al. The Interplay of Tau Protein and β-Amyloid: While Tauopathy Spreads More Profoundly Than Amyloidopathy, Both Processes Are Almost Equally Pathogenic. Cellular and Molecular Neurobiology. 2020:1-16.
5. Yiannopoulou KG, Anastasiou AI, Zachariou V, Pelidou S-H. Reasons for failed trials of disease-modifying treatments for alzheimer disease and their contribution in recent research. Biomedicines. 2019;7(4):97.
6. Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Curr Alzheimer Res. 2010;7(8):656-64.
7. Mufson EJ, Counts SE, Perez SE, Ginsberg SD. Cholinergic system during the progression of Alzheimer's disease: therapeutic implications. Expert Rev Neurother. 2008;8(11):1703-18.

8. Swerdlow RH. Pathogenesis of Alzheimer's disease. Clin Interv Aging. 2007;2(3):347-59.
9. Hadavi D, Poot AA. Biomaterials for the Treatment of Alzheimer's Disease. Front Bioeng Biotechnol. 2016;4:49.
10. Cui GH, Shao SJ, Yang JJ, Liu JR, Guo HD. Designer Self-Assemble Peptides Maximize the Therapeutic Benefits of Neural Stem Cell Transplantation for Alzheimer's Disease via Enhancing Neuron Differentiation and Paracrine Action. Mol Neurobiol. 2016;53(2):1108-23.
11. Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC. Polymeric nanoparticles for drug delivery. Methods Mol Biol. 2010;624:163-75.
12. Sánchez-López E, Ettcheto M, Egea MA, Espina M, Cano A, Calpena AC, et al. Memantine loaded PLGA PEGylated nanoparticles for Alzheimer's disease: in vitro and in vivo characterization. J Nanobiotechnology. 2018;16(1):32.
13. Ak T, Gülçin İ. Antioxidant and radical scavenging properties of curcumin. Chemico-Biological Interactions. 2008;174(1):27-37.
14. Tang M, Taghibiglou C. The Mechanisms of Action of Curcumin in Alzheimer's Disease. J Alzheimers Dis. 2017;58(4):1003-16.
15. Barbara R, Belletti D, Pederzoli F, Masoni M, Keller J, Ballestrazzi A, et al. Novel Curcumin loaded nanoparticles engineered for Blood-Brain Barrier crossing and able to disrupt Abeta aggregates. Int J Pharm. 2017;526(1-2):413-24.
16. Huang N, Lu S, Liu XG, Zhu J, Wang YJ, Liu RT. PLGA nanoparticles modified with a BBB-penetrating peptide co-delivering Aβ generation inhibitor and curcumin attenuate memory deficits and neuropathology in Alzheimer's disease mice. Oncotarget. 2017;8(46):81001-13.
17. Kuo Y-C, Tsai H-C. Rosmarinic acid- and curcumin-loaded polyacrylamide-cardiolipin-poly(lactide-co-glycolide) nanoparticles with conjugated 83-14 monoclonal antibody to protect β-amyloid-insulted neurons. Mater Sci Eng C Mater Biol Appl. 2018;91:445-57.
18. Sun D, Li N, Zhang W, Zhao Z, Mou Z, Huang D, et al. Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. Colloids Surf B Biointerfaces. 2016;148:116-29.
19. Zhang C, Wan X, Zheng X, Shao X, Liu Q, Zhang Q, et al. Dual-functional nanoparticles targeting amyloid plaques in the brains of Alzheimer's disease mice. Biomaterials. 2014;35(1):456-65.
20. Kurakhmaeva KB, Djindjikhashvili IA, Petrov VE, Balabanyan VU, Voronina TA, Trofimov SS, et al. Brain targeting of nerve growth factor using poly(butyl cyanoacrylate) nanoparticles. J Drug Target. 2009;17(8):564-74.
21. Sarvaiya J, Agrawal YK. Chitosan as a suitable nanocarrier material for anti-Alzheimer drug delivery. International Journal of Biological Macromolecules. 2015;72:454-65.
22. Kurz A, Farlow M, Lefèvre G. Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review. International Journal of Clinical Practice. 2009;63(5):799-805.
23. Nagpal K, Singh SK, Mishra DN. Optimization of brain targeted chitosan nanoparticles of Rivastigmine for improved efficacy and safety. International Journal of Biological Macromolecules. 2013;59:72-83.
24. Yang R, Zheng Y, Wang Q, Zhao L. Curcumin-loaded chitosan–bovine serum albumin nanoparticles potentially enhanced Aβ 42 phagocytosis and modulated macrophage polarization in Alzheimer's disease. Nanoscale Research Letters. 2018;13(1):330.
25. Mirzaie Z, Ansari M, Kordestani SS, Rezaei MH, Mozafari M. Preparation and characterization of curcumin-loaded polymeric nanomicelles to interference with amyloidogenesis through glycation method. Biotechnology and Applied Biochemistry. 2019;66(4):537-44.
26. Liu G, Men P, Kudo W, Perry G, Smith MA. Nanoparticle–chelator conjugates as inhibitors of amyloid-β aggregation and neurotoxicity: A novel therapeutic approach for Alzheimer disease. Neuroscience Letters. 2009;455(3):187-90.
27. Sharma B, Pervushin K. Magnetic Nanoparticles as In Vivo Tracers for Alzheimer's Disease. Magnetochemistry. 2020;6(1):13.
28. Fernández T, Martínez-Serrano A, Cussó L, Desco M, Ramos-Gómez M. Functionalization and Characterization of Magnetic Nanoparticles for the Detection of Ferritin Accumulation in Alzheimer's Disease. ACS Chemical Neuroscience. 2018;9(5):912-24.
29. Amin FU, Hoshiar AK, Do TD, Noh Y, Shah SA, Khan MS, et al. Osmotin-loaded magnetic nanoparticles with electromagnetic guidance for the treatment of Alzheimer's disease. Nanoscale. 2017;9(30):10619-32.
30. Lasagna-Reeves C, Gonzalez-Romero D, Barria MA, Olmedo I, Clos A, Sadagopa Ramanujam VM, et al. Bioaccumulation and toxicity of gold nanoparticles after repeated administration in mice. Biochemical and Biophysical Research Communications. 2010;393(4):649-55.
31. Gao N, Sun H, Dong K, Ren J, Qu X. Gold-nanoparticle-based multifunctional amyloid-β inhibitor against Alzheimer's disease. Chemistry. 2015;21(2):829-35.
32. Han X, Man Z, Xu S, Cong L, Wang Y, Wang X, et al. A gold nanocluster chemical tongue sensor array for Alzheimer's disease diagnosis. Colloids Surf B Biointerfaces. 2019;173:478-85.
33. Mutlu NB, Değim Z, Yılmaz Ş, Eşsiz D, Nacar A. New perspective for the treatment of Alzheimer diseases: Liposomal rivastigmine formulations. Drug Development and Industrial Pharmacy. 2011;37(7):775-89.
34. Spuch C, Navarro C. Liposomes for Targeted Delivery of Active Agents against Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). Journal of Drug Delivery. 2011;2011:469679.
35. Kuo YC, Tsao CW. Neuroprotection against apoptosis of SK-N-MC cells using RMP-7- and lactoferrin-grafted liposomes carrying quercetin. Int J Nanomedicine. 2017;12:2857-69.
36. Kuo YC, Lee YJ. Rescuing cholinergic neurons from apoptotic degeneration by targeting of serotonin modulator-and apolipoprotein E-conjugated liposomes to the hippocampus. Int J Nanomedicine. 2016;11:6809-24.
37. Mirzaie Z, Ansari M, Kordestani SS, Rezaei MH, Mozafari M. Preparation and characterization of curcumin-loaded polymeric nanomicelles to interference with amyloidogenesis through glycation method. Biotechnol Appl Biochem. 2019;66(4):537-44.
38. Yang P, Sheng D, Guo Q, Wang P, Xu S, Qian K, et al. Neuronal mitochondria-targeted micelles relieving oxidative stress for delayed progression of Alzheimer's disease. Biomaterials. 2020;238:119844.
39. Lu Y, Guo Z, Zhang Y, Li C, Zhang Y, Guo Q, et al. Alzheimer's Disease: Microenvironment Remodeling Micelles for Alzheimer's Disease Therapy by Early Modulation of Activated Microglia (Adv. Sci. 4/2019). Advanced Science. 2019;6(4):1970024.
40. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, et al. Dendrimers: synthesis, applications, and properties. Nanoscale research letters. 2014;9(1):247-.
41. Igartúa DE, Martinez CS, del V. Alonso S, Prieto MJ. Combined Therapy for Alzheimer's Disease: Tacrine and PAMAM Dendrimers Co-Administration Reduces the Side Effects of the Drug without Modifying its Activity. AAPS PharmSciTech. 2020;21(3):110.
42. Wasiak T, Ionov M, Nieznanski K, Nieznanska H, Klementieva O, Granell M, et al. Phosphorus Dendrimers Affect Alzheimer's (Aβ1–28) Peptide and MAP-Tau Protein Aggregation. Molecular Pharmaceutics. 2012;9(3):458-69.
43. Wasiak T, Marcinkowska M, Pieszynski I, Zablocka M, Caminade A-M, Majoral J-P, et al. Cationic phosphorus dendrimers and therapy for Alzheimer's disease. New Journal of Chemistry. 2015;39(6):4852-9.
44. Aso E, Martinsson I, Appelhans D, Effenberg C, Benseny-Cases N, Cladera J, et al. Poly(propylene imine) dendrimers with histidine-maltose shell as novel type of nanoparticles for synapse and memory protection. Nanomedicine: Nanotechnology, Biology and Medicine. 2019;17.