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UTILIZING NANOTECHNOLOGY FOR ALZHEIMER'S DISEASE THERAPY

Yousef S. Sawikr[1*], Ibrahim S. Ibrahem[2]

[1]Department of Pharmacology and Toxicology, Faculty of Medicine University of Ajdabiya, Libya.

[2]Zoology Department, Sciences Faculty, Ajdabiya University, Libya.

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***Corresponding Author: Yousef S. Sawikr**
Department of Pharmacology and Toxicology, Faculty of Medicine University of Ajdabiya, Libya.

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ABSTRACT

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles in the brain. Currently available treatments only provide symptomatic relief and do not stop disease progression. Nanotechnology offers promising opportunities to improve AD diagnosis and therapy. This review summarizes recent advances and challenges in using nanomaterials for AD treatment. Different types of nanoparticles like liposomes, polymers, nanogels, dendrimers, and antibody-conjugated nanoparticles have been explored for targeted delivery of therapeutics across the blood-brain barrier. Combining nanotherapies that delivering multiple drugs show potential for treating AD. However, issues like reproducibility, scale-up, and chronic toxicity needs to be addressed before clinical translation. Further research on multi-functional nanoparticles and exploring novel molecular targets is warranted. Overall, nanomedicine provides optimism for improved AD management but more preclinical studies are required before its clinical potential can be realized.

KEYWORDS: Alzheimer disease, blood brain Barrier Nanotherapy, liposomes, nanogels, dendrimers.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting over 50 million people worldwide. With rising life expectancy, this number is projected to reach 150 million by 2050 [1]. Pathologically, AD is characterized by accumulation of extracellular beta-amyloid (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau proteins in the brain [2]. Aβ plaques first appears in neocortical regions and later spread to the hippocampus, amygdala and basal ganglia as the disease advances. Tau pathology originates in locus coeruleus and transentorhinal regions before propagating to the hippocampus and neocortex [2]. Though the exact cause remain unknown, both early-onset familial AD and late-onset sporadic AD are associated with mitochondrial dysfunction, inflammation, and oxidative stress [3], [4]. Currently approved medications only provide symptomatic relief without stopping disease progression. Novel therapies targeting different mechanisms are needs to effectively treat AD.

The blood-brain barrier (BBB) is a major obstacle in delivering therapeutics to the brain. It is formed by specialized endothelial cells lining the cerebral microvessels, which restricts the passage of hydrophilic molecules and large compounds [5]. Receptor-mediated transcytosis enables transport of plasma proteins like insulin, transferrin, and low-density lipoproteins across the BBB. Aβ peptides crosses the BBB via receptors like LDLR-related protein 1 and advanced glycation end-product receptor (RAGE) [6]. Understanding the structural and transport properties of the BBB is essentially for designing strategies to enhance brain drug delivery for AD therapy.

Nanoparticles ranging from 1-100 nm possess unique properties like high surface area, drug encapsulation ability, and surface modification potential. Their small size facilitates interaction with biomolecules and cellular uptake compared to bulk materials [7], [8]. This make them promising candidates for bioimaging, diagnostics, and drug delivery. Different nanocarriers like polymeric nanoparticles, liposomes, dendrimers, and nanogels have been investigated for the management of CNS diseases like AD [9], [10]. The following review summarizes recent advances in the application of nanotechnology for AD therapeutics.

Nanoparticle Systems for AD Therapy

Liposomes

Liposomes are spheres composed of phospholipid bilayers that can encapsulate hydrophilic drugs in the aqueous core and hydrophobic agents within the memmebrane. Coating liposomes with nutrients like glucose improves their transport across the BBB via passive diffusion [11]. Surface modifications with proteins, antibodies, or peptides that target specific receptors on the BBB endothelium enables receptor-mediated transcytosis of liposomes into the brain [12]. Curcumin-loaded liposomes with transferrin antibody coating demonstrated enhanced brain uptake and AD therapy in animal models [13]. Mannosylated liposomes delivering ApoE2 gene reduces Aβ pathology in APP/PS1 mice, indicating their potential for AD gene therapy [14]. Overall, liposomes are biocompatible, versatile, and stable carriers that can cross the BBB through passive and active targeting.

Polymeric Nanoparticles

Biodegradable polymers like PLGA are commonly used to prepare nanoparticles for drug encapsulation. PLGA nanoparticles loaded with memantine reduces neuroinflammation and Aβ pathology in an AD mouse model [15]. Zinc-loaded nanoparticles alleviates neuronal deficiencies in AD-induced mice [16]. Lactoferrin conjugated PLGA nanoparticles containing the acetylcholinesterase inhibitor huperzine A, shows improved brain uptake and therapeutic efficacy [17]. Thymoquinone, an antioxidant in Nigella sativa seeds, shows neuroprotection in animal models of AD [18]. Encapsulating thymoquinone in polysorbate-80 coated PLGA nanoparticles enables its sustained release and brain delivery [19]. Polymeric nanoparticles thus allows tunable delivery of diverse therapeutic agents across the BBB.

Nanogels

Nanogels are crosslinked hydrogel nanoparticles that can efficiently encapsulate drugs and enhances their stability compared to free forms [20]. Pullulan nanogels prevents Aβ fibrillation in vitro, indicates their potential as artificial chaperones for AD therapy [21]. Insulin-loaded nanogels increases nose-to-brain delivery in mice, presents a non-invasive option for AD treatment [22]. Hybrid nanogels combining polysaccharides like chitosan with drugs showed high drug loading, biodegradability, and neuroprotection [17]. Overall, nanogels are emerging as promising carriers for nose-to-brain delivery of AD therapeutics.

Dendrimers

Dendrimers are repetitively branched polymeric nanostructures with tunable surface functionality. Low generation dendrimers conjugated with lactoferrin improves brain delivery and efficacy of memantine in an AD mouse model [23]. Dendrimer encapsulation also reduces the toxicity of acetylcholinesterase inhibitors like tacrine [24]. The high solubility and bioavailability offered by dendrimers makes them attractive for delivering drugs across the BBB to treat CNS conditions including AD.

Antibody-Targeted Nanoparticles

Antibody-conjugated nanoparticles can specifically bind to target proteins like Aβ aggregates and promote their clearance. Chitosan nanoparticles coated with Aβ antibody fragments shows increased uptake in amyloid-containing neurons [25]. Superparamagnetic iron oxide nanoparticles coupled with Aβ antibody exhibits diagnostic potential for early AD detection [26]. Thus, antibody-directed nanoparticles can enable selective targeting of disease pathology while avoiding off-target effects.

Receptor-Mediated Targeting Strategies

Receptor-mediated endocytosis pathways can be exploited to enhance brain uptake of nanoparticles. Transferrin receptor is highly expressed at the BBB endothelium and has been used for receptor-mediated delivery of AD therapeutics [27]. Similarly, nanoparticles conjugated with insulin or lactoferrin receptors showed improved targeting and therapeutic efficacy in AD models [17], [27]. Overall, functionalizing nanoparticles with receptors highly expressed at the BBB allows improved transport into the brain.

Combination Nanotherapies

Single target therapies have shown limited success in AD treatment. Combining nanoparticles loaded with different therapeutic molecules like tau inhibitors, anti-amyloids, and antioxidants may offer better clinical outcomes. A multifunctional nano-probe delivering an anti-amyloid agent and MRI contrast agent enabled simultaneous AD therapy and diagnosis [28]. Curcumin and T807 loaded red blood cell membrane coated nanoparticles showed synergy in ameliorating tau pathology [29]. Although still early, multi-drug nanocarriers present an emerging opportunity for multimodal AD therapy.

Gene Therapy

Gene therapy aims to introduce genes encoding therapeutic proteins like enzymes or growth factors. Nanoparticles are explored as non-viral vectors for gene delivery as they offer advantages like low toxicity, payload protection, and tunable release [30]. Dendrimers improved brain uptake of plasmid DNA encoding BDNF, leading to neuroprotection in an AD model [31]. Overall, nanotechnology provides a versatile platform for targeted gene therapy, which remains a promising approach for neurodegenerative conditions like AD.

CHALLENGES AND FUTURE OUTLOOK

While nanomedicine provides optimism for AD therapy, some key challenges need to be addressed. Large scale reproducible synthesis and quality control remains difficult for most nanoparticle systems. Predicting their biodistribution and toxicology profiles is also complex. Most preclinical studies use young animal models which do not replicate age-related neuropathy and BBB changes in AD patients. More relevant transgenic models and human cell-based models are required to better predict clinical translation potential. Moving forward, designing nanoparticles with multiple functionalities like drug delivery, imaging and biomarker detection can provide theranostic platforms for AD. Exploring novel molecular targets like mitochondrial function and neurogenesis pathways could offer new opportunities for therapeutic intervention. Overall, continuous development of innovative nano-bio interfaces tuned to the pathophysiology of AD can enable earlier diagnosis and enhanced combinatorial therapy, providing a pathway to effective disease management!

CONCLUSION

Nanotechnology offers innovative solutions to improve drug delivery and therapy for AD. Different nanoparticle platforms like liposomes, polymeric nanoparticles, nanogels, and dendrimers have shown promise for encapsulating and delivering diverse therapeutic agents into the brain. Combination and receptor-targeted nanotherapies further enhance selectivity and efficacy of AD treatment. However, challenges related to scale-up, toxicity, and validating efficacy in appropriate disease models remain. Further research on multi-functional nanosystems capable of modulating novel pathways deregulated in AD is needed to realize the full clinical potential of nanomedicine for AD therapy.

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