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Mini Review

Application of Nanotechnology of Treatment Modalities for Alzheimer's disease

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ABSTRACT

Alzheimer's disease is primary neurodegenerative pathology of unknown etiology and influenced by several factors with characteristic neuropathological and neurochemical features. Currently, drugs approved for the treatment of this disease only allow relieving symptoms and are accompanied by several side effects. Nanotechnology appears as an alternative for the treatment of Alzheimer's, as it offers many advantages to modern medicine allowing a non-invasive and targeted diagnosis and treatment, reducing adverse reactions and systemic effects. The article aims to recognize the potential of using nanoparticles in the treatment of Alzheimer's disease, identifying the most promising treatments and their possible side effects. Gold nanoparticles are capable of crossing BHE, carrying essential drugs to inhibit the aggregation of peptides, as well as dissolve pre-existing fibrilla. Biodegradable and biocompatible polymers, such as polyglycolic polylactide (PLGA), are a promising and safe approach and have been widely used. The best techniques are those that guarantee that nanoparticles are capable of crossing the BHE, reach their therapeutic target, as well as guarantee that these particles do not induce toxic effects in the body. Although nanoparticles are able to treat some diseases efficiently, little is known about their side effects; they may or may not be more harmful to the body than the disease they intended to treat. There are several promising therapeutic approaches, but none has yet been approved, since it is difficult to maintain adequate drug concentrations in the intraneuronal space. Establishing the toxic dose is necessary for the approved use of a nanoparticle in a treatment, but it is almost impossible to predict its cytotoxic effects in extraneuronal regions.

Keywords: Alzheimer's disease; Nanomaterials; Nanotechnology; Toxicity

INTRODUCTION

Alzheimer's disease (AD) is an acquired neurodegenerative disease leading to a progressive and untreatable cognitive and behavioral impairment. The pathogenesis of AD is associated with the formation of amyloid-β plaques extracellularly and neurofibrillary tangles intracellularly. These induce neuronal cell death and the loss of synapse which is initiated first before progressively leading to the cognitive deficit. AD being known as the commonest form of dementia amongst the elderly population can however present itself in two forms which are the rare early-onset dementia leading to AD occurring before the age of 65 and the common late-onset AD or known as senile dementia occurring after the age of 65 due to aging. AD is usually the cause of plaque formations in the hippocampus of the brain that is responsible for encoding memories, as well as other parts of the cerebral cortex that is crucial for proper judgements and making decisions. Besides cognitive impairment such as memory loss, the impairment in behaviors can be seen through common neuropsychiatric symptoms such as depression, agitation, delusion, and hallucinations [1].

There are various drugs available that aim to target in treating AD; however, the most common drawback is due to the blood-brain barrier (BBB). Due to the lack of effective therapeutic medicine available to treat AD, hence only symptomatic treatment is being given to AD patients. However, in recent years, the development of nanotechnology has shown great potential in overcoming this limitation. Nanotechnology involves the modification or development of desired materials with structures sized between 1 and 100 nanometers. Nanomaterials have a large surface area and its high surface to volume ratio is highly advantageous as it has significant effects on its structure. The properties of nanomaterials are lighter, stronger, faster, smaller, and more durable hence potentially making it a promising material for drug delivery especially in the case of treating cancer and AD [2]. Hence, in this review, we will discuss how nanotechnology can be used as a

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potential therapeutic strategy for Alzheimer's disease.

THERAPY FOR ALZHEIMER'S DISEASE

In order for a drug to have its maximum therapeutic effect, it is important for the drugs to retain its bioavailability, pharmacodynamics, and pharmacokinetics. Hence, the integration of a drug into or onto a polymeric and/or lipidic nanoparticle (NP) is aimed at greatly enhancing the pharmacotherapy effect of a drug. The use of NPs is beneficial in drug delivery process as it increases the bioavailability of a drug by improving the aqueous solubility and increases the drug half-life which in turn reduces the rate of drug clearance as well as delivering the drug to its targeted site of action. As mentioned previously, the main limitation for drugs in AD treatment is due to the blood-brain barrier (BBB); hence, it is important to recognize the structure and functionality of the BBB to be able to propose different alternatives to deliver AD drugs via the nanodrug delivery system [3]. The utilization of the binding affinity of lipid-soluble NPs towards the endothelial cells can amplify the rate of transport of a drug via endocytosis or lipophilic transcellular pathways. Besides that, the adsorptive characteristic of NPs can be advantageous as it can adsorb onto the blood capillaries of the BBB thus increasing the probability for the target drug to be transported beyond the barrier. Furthermore, the modification of NPs with specific receptors can enhance the uptake of drugs across BBB through carrier protein and receptor-mediated transcytosis. Despite the ability of NPs to permeate the BBB, only about 5% drug is able to reach the brain with the existing 95% of the drug at the inexact site of action which may lead to potential systemic side effects as the conventional route of administration of drugs fails to deliver the agent to the brain accurately. However, intranasal administration of drugs has been shown to facilitate the delivery of therapeutic agents directly to the central nervous system (CNS) via the olfactory and trigeminal nerves of the nasal cavity. In addition, intranasal administration is safe and noninvasive and the drug is able to surpass the hepatic first-pass metabolism as well as drug degradation which will increase the bioavailability of the drug [5].

The delivery of AD therapeutic protein or peptide functions in the same mechanism as the delivery of AD drugs, in which the protein or peptide is encapsulated or integrated to a NP or via the attachment to polyethylene glycol. The principle involved in the delivery follows the nanodrug delivery system, in which the association of a protein or peptide to NPs enables the protein or peptide molecules to cross the BBB. The intranasal administration is believed to be the most ideal route of protein or peptide delivery to the target site of action. This route allows the therapeutic agent to be directly transported to the CNS without passing through the gastrointestinal tract or blood, thus safeguarding it from proteolytic degradation. Based on several researches carried out on AD rat models, the delivery of proteins or peptides using NPs has conclusively proven to be a stable, effective, and safe treatment for AD. Nevertheless, this delivery system has its own set of limitations such as high cost, limited or unstable bioavailability, and some toxic effects.

Several studies have hypothesized that the mitochondria play an important role in the pathophysiology of AD. The reduction of brain metabolism or increased reactive oxygen species causes mitochondrial dysfunction which eventually leads to the apoptosis of nerve cells in the brain thus accelerating neurodegeneration. Consequently, one of the approaches that are currently being focused on the treatment of AD is by targeting the production of neuronal ROS by the mitochondria [6]. The inner mitochondrial membrane is highly selective and blocks the entry of most molecules. Some of the potential strategies include conjugating ROS scavengers to a mitochondrion penetrating short peptide sequences that has distinct physicochemical properties to transport the ROS scavengers across the inner mitochondrial membrane; encapsulating antioxidant in lipidic NP to promote antioxidant intake via micropinocytosis; and conjugation of therapeutic agents with mitochondrial signal peptide to improve the recognition of transporters for mitochondrial delivery. The antioxidant NP that is used to treat AD is known as ceria NPs. It was observed in research that positively charged TPP-ceria NPs are able to localize into the mitochondria in various cell lines and at the same time scavenge mitochondrial ROS efficiently to reduce oxidative stress thus capable of suppressing neuronal death in tested mouse model. The evolution of nanomedicine and mitochondrionspecific nanotechnology approaches is shown in Gene therapy is a technique that is carried out to intracellularly deliver genetic materials to elucidate a healing effect by compensating the mutated gene such as DNA or RNA. This form of therapy is aimed at replacing or correcting the mutated gene through a single [7].

Immunotherapy is an emerging potential solution for the treatment of cancer. The principles and design of immunotherapy are straightforward as it firstly begins by extracting the T cells of cancer patients for in vitro reconstruction, allowing them to be targeted to specific cancer receptors. These modified T cells are then reintroduced into the patient resulting in tumor cells to undergo apoptosis in the blood circulation without causing any adverse reactions. However, one of the main drawbacks of immunotherapy is that it can prevent the immune system-mediated tumor elimination due to the progression of tumor malignancy followed by immune suppression of the patient. Besides that, the modified and reconstructed T cells might not be completely safe for human use. Nanotechnology or nanoparticles is a suggested alternative that has the ability to overcome these limitations and hence the increasing success rate of immunotherapy by making it safe and effective.

The Limitations of Nanotechnology There are several consequences that were discovered in the application of nanotechnology especially in the medical field. The solubility of NPs may differ in certain conditions such as varying temperatures. The changes in temperature can influence the interaction between NPs and the drug. This can cause certain patients to encounter different therapeutic impacts which are undesirable for medical treatments. Therefore, these aspects need to be emphasized in future research of nanotechnology in AD diagnosis or therapy to bring about favorable outcomes.

The administration route of NPs may affect the bioavailability of the drug that is delivered to the body. Nasal administration route is the most practical and admissible as it is one of the most noninvasive methods to administer drugs into the human body. However, the nasal cavity has enzymes that can highly affect the bioavailability of the drug. Thus, this may require increasing the dosage of the drugs when administering which can cause adverse reactions in the nasal mucosa as the nasal cavity has a limited capacity of drug concentration. Therefore, it is important to administer a low concentration of drugs via the nasal route. Besides that, when introducing a high volume of low bioavailable drugs, this can cause serious respiratory effects such as chronic inflammatory responses, peribronchial inflammation, and oxidative stress. The blood-brain barrier plays an important function in neuronal circuits and

synaptic transmission. However, it remains to be an impenetrable obstacle for a large number of exogenous substances such as drugs including antibiotics, antineoplastic agents, and a variety of central nervous system active drugs especially neuropeptides [8]. Drug delivery using NPs is one of the possibilities to transport active molecules efficiently across the BBB. This is due to ligands that are functionalized onto NPs to improve the targeted drug delivery to overcome BBB. However, the efficiency of these ligand-modified NPs needs to be evaluated as it still requires a long blood-residency time to be able to pass through the BBB and hit their target system.

Certain NPs that have been administered into the body cannot be easily removed by various clearance systems. This may cause the NPs to accumulate within the brain system causing to cytotoxicity. Long-term accumulation of NPs in the brain may lead to brain injuries. The sink effect of NP-mediated initiation, the frequency, and intervals between injections is one of the limitations that should be considered as well. An excessive amount of dose may cause adverse effects, which in turn initiates an immunogenic response causing the alteration of NP pharmacokinetics and diminishing its efficacy. Besides that, neurotoxicity caused by NPs may be due to its physicochemical properties such as size, shape, and surface area. These factors could potentially modulate or interfere with the transport of hemostatic mediators. The size of NPs may increase the possibility of aggregation which can interfere and block the blood flow that may result in undesirable reactions in the lungs, heart, and other microinfarctions. Although nanotechnology-based approaches have shown immense therapeutic potential, it is still in its early stage. The safety and chronic effects of NPs should be investigated further to ensure it is clinically safe and effective for the treatment of human diseases.

ADVANCES IN NEUROLOGY USING NANOTECHNOLOGY

The applications of nanotechnology in neurological therapy involve cellular biology. There are diverse therapeutic options available for neurological disorders even for incurable Alzheimer's disease and Parkinson's disease. Since there is an increase in scientific researches and research funding, the future explorations of nanotechnology in neurological disorders seem very promising. The prospects of nanoneurotechnology mainly focus on regenerative medicines. Besides that, stem cell research is an essential aspect in nanoneurotechnology. Neurodegenerative disorders are mostly provoked by ceased blood supply to tissues and reactive oxygen species. Hence, the current progression of treating neurodegenerative diseases involves inhibiting these conditions [9].

Nanomaterials are functional biological elements that exist in a nanometer range. This ensures a better interaction for the elements with the biological system. The fundamental principle of nanoneuromedicine is that the NPs enhance tissue regeneration without stimulating an immune response and warding off infections. A few of the prominent usage of NPs in stem cell research includes magnetic NPs in the isolation and assortment of stem cells. Quantum dots are also used in molecular imaging and tracing of stem cells. The regulation of stem cell proliferation and differentiation can also be controlled by using NPs. Organ failures remain as one of the most dreaded medical issues. Scaffolds are an important aspect of tissue engineering. Natural scaffolds are obtained through a process of decellularization while retaining the original composition of the extracellular matrix to allow recellularization using induced pluripotent stem cells, which can refurbish the functionality of organs. Stem cells maintain and generate tissues in the body and go through selective differentiation to become specialized cells. This enables stem cells to be integrated with NPs for improved cell proliferation and differentiation. Nanomaterials can also enhance the optimal control of microenvironment conditions of transplant cells. The harvested stem cells can be developed into 3-dimensional organoids. Brain studies are always hindered by limitations due to the usage of postmortem tissue. This venture can pave the way for future functional studies of the human brain. Regeneration of stem cells has to be continuously monitored and evaluated to ensure its functional and structural accuracy. Nanoparticles can also be used in confocal imaging to evaluate the bioengineered tissue. Further developments in this field have brought upon the evolution of a new branch of research which is nanotoxicology. This is because the toxicity of nanomaterials needs to be verified before the application of clinical trials [10].

CONCLUSION

The application of nanotechnology in the treatment of Alzheimer's disease includes the improvement of the drug, therapeutic protein, and antiamyloid delivery across the blood-brain barrier. In addition, the transport of antioxidants to the mitochondria to prevent the release of reactive oxygen species and delivery of genetic material to the cells are also the implementation of nanotechnology in Alzheimer's disease treatment. The prospects of nanotechnology in the treatment of Alzheimer's disease include advances in bioimaging and proteomics. Despite recent advancements in using nanotechnology for the treatment of Alzheimer's disease, the possibility of chronic toxicity has to be further researched for future clinical applications. Another big challenge in utilizing nanotechnology in Alzheimer's disease is the cost. The cost would be a barrier in accepting nanotechnology treatment as the common treatment for Alzheimer's disease.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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