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REVIEW ARTICLE

Polymeric nanoparticles in the treatment of neurodegenerative diseases: an overview

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Abstract

This article present review of literature covering the use of numerous polymeric nanoparticles in the treatment of neurodegenerative disorders. It also throws a light on the barriers that hinder the delivery of drug to brain, the reasons for ineffective therapeutic action of drugs for treatment of NDs and why nanoparticles are preferred for treatment of neurodegenerative diseases. The blood brain barrier is main boundary that covers the brain and separates the neural tissues from circulating blood. It not only maintains homeostasis of brain but also obstructs the movement of drug molecules to brain. Due to this reason the CNS diseases cannot be treated properly. The incidence of neurodegenerative diseases is increasing with increasing population. Some of the most common NDs are Alzheimer disease and Parkinson disease. The barrier in the diagnosis and treatment of NDs is blood brain barrier. So, to overcome this problem attention is diverted to develop such novel drug delivery system that can carry dug to brain and can increase bioavailability in brain. Nanotechnology particularly use of nanoparticle can provide development in treatment of NDs.

Keywords

Blood brain barrier
Nanotechnology
Neurodegenerative diseases
Pathophysiology
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Introduction

Neurodegenerative disorders involved CNS related diseases that affect 30 million people globally (Sheikh et al., 2013). There are two types of neurological disorders. Neurological disorders belong to neuropsychiatric category include neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, dementias, and multiple sclerosis, as well as neurological disorders belong cerebrovascular accident (CVA) (Honjo et al., 2012). It is believed that neurodegenerative disorders are mostly caused by the permanent loss of neurons in both structure and function which inevitably leads to their death. Patients' cognitive, motor, mental, and sensory functions all suffer as a result of this deterioration. The most common neurodegenerative disease is Alzheimer's disease (AD) while Parkinson's disease (PD) is the 2ND most common ND (Hernando et al., 2013) Transmissible spongiform encephalopathy (TSE), huntington's disease (HD) and multiple sclerosis (MS) are some of the less popular NDs (Stopschinski et al., 2017). These neurodegenerative disorders have a pathogenesis that starts in multiple brain regions and includes a specific brain network. Different evidence suggests that transcellular proliferation of protein aggregation is the cause of pathogenesis in various NDs such as Alzheimer's disease, Parkinson's disease and Huntington's disease (Pehlivan, 2013).

Prevelance and epidimiology: Neurodegenerative diseases are becoming more common as the population ages, and no treatment has yet been discovered. The multisystemic aspect of NDs causes a slew of problems

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in their care. This condition necessitates very costly treatment, which costs more than a hundred billion dollars per year. For example, Alzheimer's disease affected approximately 5.4 million people of all ages in America in 2012, with 13% of those suffering from the disease being 65 or older (Hagan et al., 2016). Women make up two-thirds of the 5 million people living with Alzheimer's disease. Annually, the United States spends $226 billion on Alzheimer's disease treatment. Of the top ten diseases in America, Alzheimer's disease is one of the most common ND which leads to cause of death, with no known prevention or treatment. By 2050, the number of people aged 65 and up with Alzheimer's disease is expected to have doubled. According to estimates, someone in the United States will contract this disease every 33 seconds by 2050 (Abbott, 2013). According to the 2015 World Alzheimer survey, 46.8 million people worldwide suffer from dementia, with that figure predicted to grow to 74.7 million by 2030 (Saraiva et al., 2016).

Less effective treartment and reasons: The global rise in lifespan has been resulted due to increase in the prevalence of Alzheimer's disease (AD), stroke and Parkinson's disease (PD), which has a direct effect on society and the economy. However, most of currently available treatments are symptomatic and do not improve quality of life or mitigate disease-related harm. There has been no substantial progress in the search for new drugs, and drug delivery to the CNS is a major goal to be reached (Loureiro et al., 2016).

Drugs have being formulated to treat CNS diseases but they face difficultly in crossing the blood-brain barrier and reaching the aimed site of the brain. For NDs research on drug has risen significantly in last few years, but long time has been taken to market a drug for the treatment of them. It is primarily due to insufficiency of an effective target drug delivery mechanism that can ensure effectiveness at the target site through the blood brain barrier (Patel et al., 2012). The BBB protects the brain from infectious agents such as bacteria as well as blood changes. Endothelial cells' close junctions form this barrier. Only very small and highly lipid soluble components can pass through this barrier. A significant number of active compounds have little effect in vivo due to low bioavailability in the brain. As a result, developing novel drug delivery technologies is critical for therapeutic purposes.

Colloidal carrier systems have been designed to address this issue. Poly (lactic-co-glycolic-acid) (PLGA) nanoparticles are one of the most researched vehicles for delivering drugs to their target sites (Sarkar et al., 2017).

Use of nanoparticle for neurodegenerative disorders: The delivery of therapeutics to the brain in the CNS presents a particular challenge. The blood-brain barrier limits the passage of systemically distributed therapeutics, while the extracellular matrix of the brain limits the delivery and durability of locally delivered drugs. Over the last 40 years, polymeric nanoparticles have been shown to be the solution of these problems in studies, but they are useful in local and systemic drug delivery to the CNS. Most of the polymers used in nanoparticle formation are categorized as biodegradable, biocompatible and non-toxic, enhancing the clinical utility of this technique. Nanoparticles have the ability to carry proteins, nucleic acids, and diagnostic agents in addition to small molecule drugs (Chen & Liu, 2012).

The binding of drugs to NP are more insusceptible to reticuloendothelial system phagocytosis and degradation (Masserini, 2013).

Barriers of nervous system: A vital organ of the body and core of the nervous system is brain which is shielded from the outside world by two anatomical and biochemical barriers. The main barriers are blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSF). BBB has a complex structure that protects the brain from invasive organisms in the bloodstream, as well as diseases and injuries. It does, however, greatly impede drug delivery to the brain, which prevents the treatment of many neurological conditions (Abbott, 2013). The BBB is designed to hold the brain in a state of homeostasis by allowing only those molecules to move through that are needed for brain function. This is an impenetrable and highly selective membrane that prevents drug molecules from reaching the brain (Engelhardt & Ransohoff, 2012).

Sites of barrier layer: These layers of barriers can be found in three main sites present in the nervous system. The endothelium of parenchymal micro vessels, the epithelium of the choroid plexus, and the arachnoid epithelium were the first to be affected. Tight junctions are present at each of these locations, preventing small molecules and ions from penetrating and forming a physical barrier. Toxins are metabolised by the extracellular and intracellular enzymes, which create an enzymetic barrier that protects the body (Hwang & kim, 2014). The neurovascular unit and endothelial cells regulate leukocyte movement and form an immunological barrier (Banks, 2016).

Blood brain barrier (bbb): BBB helps to preserve brain homeostasis by separating extracellular fluid from systemic blood supply. It is made up of tight endothelial cells (Sharma et al., 2015). One of the most dangerous barriers in the management of brain disorders is the blood-brain barrier (BBB). It prevents absorption of most large molecules in the CNS, such as peptides and protein drugs (Morimoto et al., 1987). The most difficult problem in the production of drugs for the management of CNS related disorders is achieving proper absorption across the blood-brain barrier. According to research conducted over the last few decades it is evaluated that blood brain barrier is a complicate structure, is versatile, and also regulates transmission of substrates between

blood and CNS. By interacting with other CNS cells and following their action, the cells involved in CNS structure serve the needs of the CNS. The blood-brain barrier's ambiguity explains the difficulty in developing drugs that can cross it, but it also provides various methods for development of drug (Novakovic et al., 2014). The BBB provides nutrients to the brain, and also prevents several substances from entering the brain from the bloodstream while it acts as a diffusion barrier. The peripheral capillaries enable free movement of components between cells, while the BBB physically and metabolically blocks the entry of molecules into the brain. The tight junction is part of the physical barrier, while the metabolic barriers are enzymes. Drug transmission to the central nervous system is restricted in the existence of the BBB. As it is a rate limiting step in determining drug permeation into the brain (Ochocinska et al, 2016).

BBB is an active interface between the brain and the periphery. And although the BBB helps to preserve tissue homeostasis, it also makes difficulty in delivery of drug to the CNS (Engelhardt & Ransohoff, 2012).

The role of the blood brain barrier varies across life, depending on the needs of the CNS and the severity of the disease (Cai et al., 2016). A material will only pass through the BBB if it is presented to it, and this presentation is determined by the substance's physicochemical properties. Since most substrates have a short half-life due to which their absorption in CNS is decreased, raising the half-life of substances will increase BBB penetration (Coureuil et al., 2017).

Structure of blood brain barrier: The BBB is made up of approximately 600 km of capillaries produced by specialized endothelial cells inside the neurovascular unit.

Three functional layers are present between blood and brain, which are astrocytes, pericyte, brain endothelial cells (BECs) and basement membrane, and has a complicated structure. Brain endothelial cells have more close linkages and no structure (Ducray et al., 2017). The astrocytes and pericytes are important for maintaining integrity and tightness of BBB Craparo et al., 2011).

Nanotechnology: Nanotechnology is a most captivating technology that exists on a nanometer scale below 100nm. This technique is projected in the development of various material devices and systems that are use in various biomedical applications.

The human being is approximately made up of very small sized cell (10μm) and proteins (5nm). The contrast of various molecules size suggests the proposal for the use of nanoparticles. NPs are used as a very small probe which is being investigated at cellular level (Bhavna et al., 2014).

In recent years use of nanoparticle is increased in fields of cosmetics, agriculture, food production and medicine has increased enormously (Zhang et al., 2013). Nanoparticles are those particles that range in size from1 to 1000 nm (1 μm) having macro-molecular materials in which the drug or biologically active material is dissolved, entrapped, or encapsulated (Cai et al., 2016).

Many synthetic polymers are being used in preparation of nanoparticles polylactides (PLA), poly (lactide-co-glycolide) PLGA, polyglycolides (PGA), polyanhydrides, polycaprolactone and polycyanoacrylates which are synthesized by various methods such as include nanoparticles of polylactides (PLA) and poly (D,L lactide-co-glycolide) (PLGA) by emulsification-diffusion and precipitation method while poly (alkyl cyanoacrylates) nanoparticles by nanoprecipitation method (Zhang et al., 2013).

Use of polymeric nanoparticles: Various materials are used for target drug delivery. Basically, the drug is embedded in the core of polymer matrix in polymeric nanoparticle formulation (Sheikh et al., 2013). Over the last few years, polymers are particularly manufactured for sustained discharge of drug and for degradation within the body. They are administered via systemic manner due to nanometer size of polymers and easily reach to site of action. These formulations are also safe active drugs from being degradation of enzymes. Mostly drugs with lipophilicity are soluble in polymers. These polymer nanoformulations have long duration of action due to sustained release of drug. They directly target the blood brain barrier and increase the pharmacological effect of drug in CNS. By increasing bioavailability, these nanoformulations decreases adverse effects and improve the patient compliance.

Strategies of nps mediated uptake of drugs into brain: The retention time of nanoparticles in blood capillaries of brain increased which increased the adsorption of drug and enhanced delivery of drug across the endothelial layer. Further it results in improved transport of drug to BBB.

Nanocarriers cross BBB via active transport. Mostly NPs target nervous system via receptor mediated endocytosis or transcytosis which involves interaction of ligand loaded nanoparticle with specific receptor, formation of vesicles within cell which phagocytes nanoparticles, transport of materials across blood brain barrier and release of nanocarriers in parenchyma cells of CNS.

Receptor mediated transport has some limitations because they need a tight junction between ligand and receptor which further result in reduce exocytosis process. On different animal models *in vivo* studies has been done which reveals that high concentration of nanoparticle is found in capillary endothelial cell in contrast to CNS parenchyma. It is also observed that saturation mechanism occur due to linkage of ligand with receptor which further reduces the competence of receptor mediated transcytosis. Carrier mediated pathway is substrate selective pathway and it delivered

Table 2: List of patents granted for nanoparticles use in neurodegenerative diseases

Nano-Formulation	Patent	Referance
Gold loaded Nanoparticles (AuNPs)	US2011262546 (Tang & Taghibiglou, 2017)	(Henchcliffe & Severt, 2011)
Nanoparticle	US2011195125 (Gilbert, 2014)	(Kulkarni et al., 2015)
High density lipoproteins loaded nanoparticles (HDL-NPs)	WO2011044545 (Holtzman, 2011)	(Osona-Núñez et al., 2011)
Solid lipid nanoparticles (SLNs)	US2011208161 (Erkkinen et al., 2018)	(Ho et al., 2011)
Magnetic nanoparticles (MNPs)	US2011213193 (Newland et al., 2016)	(Jellinger & Attems, 2011)

closely resembled endogenous carrier substrate such as glucose, aminoacids and nitrogenous bases to brain (Sheikh et al., 2013).

Normally polymeric nanoparticles are delivered systemically and their ability to cross BBB is poor but when polymeric nanoparticles are coated with polysorbate 80 they show increase permeability across BBB (Honjo et al., 2012).

Pathophysiology of neurodegenerative disorders

Alzheimer disease: Alzheimer disease (AD) is a critical neurodegenerative disorder categorized by impairment of memory and motor neurons, anxiousness, lack of understanding and severe mood fluctuations. Dementia is a major reason of Alzheimer disease in elderly patient (Banks, 2016). Clinically, AD is characterized by continuous loss of memory. Histopathological changes occur due to production of senile plaques because amyloid β peptide deposits on intracellular neurofibrillary tangles of hyperphosphorylated tau protein and extracellular membrane in brain (Hernando et al., 2016).

The important histological features of this disease are neuronal loss, neurofibrillary tangles, senile plaques, and deposition of cytosolic lipid. The neuronal loss and synapse result in atrophy of cerebral cortex and subcortical region (Stopschinski & Diamond, 2017).

The Amyloid β peptide is one of the most significant toxins in pathogenesis of Alzheimer disease. Non-selective distribution of drug in CNS and limitations to cross BBB is considered an effective therapy for treatment of AD (Pehlivan, 2013). The exact mechanism of AD is unclear; however there are numerous procedures which are under clinical trials and one of the most acceptable procedures is to direct target the production and clearance of amyloid β (Hagan et al., 2011).

Alzheimer disease is the term given to pathological entity while Alzheimer dementia is use to describe the clinical phenotype (Abbott, 2013).

Parkinson disease: For the first time in 1817, James Parkinson explained Parkinson disease (Saraiva et al., 2016). Globally, it is considered second major neurodegenerative disease (Loureiro et al., 2016). The prevalence of PD is apt to increase by increasing aging population and longevity *(*Patel et al., 2012). PD is recognized by decline in dopamine concentration in nigrostriatal pathway which results in tremors, rigidity, postural abnormalities, and bradykinesia (Sharma et al., 2015). In substantia nigra, reduction of dopamine at cellular level leads to formation of lewy bodies. These are cytoplasmic inclusion and composed of α synuclein, fibrils and ubiquitins (Novakovic et al., 2014). The exact reason of PD is not known but various factors caused growth of Parkinson disease like inflammation of neurons, misfolding of protein and generation of reactive oxidative species (ROS) (Ochocinska et al., 2017). Mild dementia also develops in person affected with PD. Dopamine agonist includes apomorphine, cholinesterase inhibitors like donepezil and mono amine oxidase type B inhibitors are being used in treatment of PD (Bhavna et al., 2014).

Lewy body dementia: Lewy body dementia is 2nd kind of dementia which leads to cause mental abnormality. LBD is recognized by variations in attention and alertness, visual hallucinations, muscles rigidity and tremors (Salata, 2004). The formation of lewy bodies and neuritis are signs of LBD (Coureuil et al., 2017). Sometimes, it is considered that LBD is similar to dementia which is caused by either AD or PD. The LBD has acute and rapid duration of action as compared to AD (Ducray et al., 2017).

Fronto-temporal dementia: The shrinkage of temporal and frontal interior lobes in brain is linked to frontal temporal dementia. This disease shows various behavioral changes such as change in personality, social functioning, and loss of interest or excitement and language problems (Craparo et al., 2011). FTD having microscopic Pick bodies affected various parts of brain. These are abnormal protein filled structure developed in neurons. Histologically, FTD is characterized by neurofibrillary tangles (NFT) of Tau protein in brain (Bhavna et al., 2014).

Role of nanoparticles in the treatment of nds: Various neurodegenerative disorders, for prevention and therapeutic strategies focus on clearance of aggregated protein plaques from brain, inhibition of protein fibrillation and lowering of protein aggregation induced toxicity (Sarkar et al., 2017).

Alzheimer disease: There are numerous factors involved in ineffective treatment of Alzheimer disease. The first factor includes the complexity of brain which makes AD treatment difficult. Numerous molecular and cellular events are involved in the death of specific neurons in AD (Salata, 2004). At present time no method is available for the treatment of effects caused by AD. The symptomatic therapy is accessible (Zhang et al., 2014). Mostly ingestible drugs do not reach to the brain due to inadequate absorption and are completely metabolized by liver. Main barrier in the treatment of AD is the BBB because it inhibits the absorption of all macromolecules and 98% of micromolecules. The use of nanoparticles is one of the most useful strategies to overcome the barriers and it increased bioavailability of therapeutic agents (Masserini, 2013). It is observed in one previous study that Rivastigmine is an appropriate substrate for brain by use of PLGA and PnBCA NPs as carrier which lead to cause the fast reverse of memory loss in mice in contrast to rivastigmine alone (Fornaguera et al., 2015). Ceriumoxide nanoparticles (CeONPs) are use as therapeutic agent in the management of neurodegenerative diseases because they reduce oxidative stress (ROS) in damaged neurons. CeONPs also altered brain-derived neurotrophic factor and further delay the apoptosis in neurons. These NPs in conjugation with metal chelators and PEG also reduce Aβ aggregation after coatings (Erkkinen et al., 2018).

Parkinson disease: Numerous nanoparticles of dopamine agoinst are developed for attaining dopaminergic stimulation and it provides long time safety (Gomes et al., 2014). In Parkinson disease, nanoparticles of ceriumoxide (CeNPs) decrease the neurons damage which caused due to exposure of manganese but these NPs maintain the metabolism of neurotransmitters such as catecholamine and dopamine (Tosi et al., 2016).

In one study it is evaluated that alpha-synuclein specific monoclonal antibodies modified with polybutylcyanoacrylate nanoparticles are very useful in treating neurodegenrative disorders. The nanoformulation of bromocriptine loaded solid lipid nanoparticles (SLNPs) also shows activity against Parkinson (Spuch et al., 2012). The dopamine encapsulated PLGA nanoparticles are found to be helpful in treating Parkinson disease. Dopamine nanoparticles show sustained release of dopamine which reduce dopamine clearance in plasma alongwith decrease dopamine autoxidation (Mignani et al., 2017).

Lewy body dementia: As LBD is it closely resembles to both PD and AD so diagnosis of LBD is quiet difficult (Mittal et al., 2011). The cognitive symptoms in LBD are treated by cholinesterase inhibitors. This drug was discover for AD treatment but later on researchers found that LBD patient show positive response to this drug as compare to AD patient. It is also observed that levodopa which is a PD drug is used to treat movement symptoms in LBD. The pathological characrterization of LBD is abnormal accumulation of α synuclein (Bhavna et al., 2014). There is no effective nanocarrier method developed for treatment of LBD. However, it can be treated by change of irregular accretion of alpha-synuclein in brain. The preparation of phospholipid nanoparticle consisting phosphatidylglycerol has neuroprotective effect in LBD and PD (Patel et al., 2012). Polyamidoamine (PAMAM) dendrimers shows inhibitory effect on fibril formation and causes inhibition of alpha-synuclein fibrillation (Dong et al., 2012).

Conclusion: Numerous strategies are available for the treatment of neurodegenerative diseases. Blood brain barrier is the main hindrance in treatment of NDs. The development of direct target delivery system has been effective in treating NDs but pharmaceutical and academic community faces this challenge. Nanotechnology is considered the most promising and effective approach. Nanoparticles with different physicochemical properties have a variety of applications in biomedicine. Various neuroactive agents such as drugs, genes, and growth factors are modified with nanoparticles. These modified nanoformulations are helpful in the delivery of neuroactive agents in brain. Such nanoparticles enhance the transport of drugs to brain by reducing adverse effects, enhancing half-life of drugs, and reducing the frequency of administration of drug.

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