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Treatment of Neurodegenerative Disorders through the Blood-brain Barrier using Nanocarriers

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Abstract

Neurodegenerative diseases refer to disorders of the central nervous system (CNS) that are caused by neuronal degradations, dysfunctions, or death. Alzheimer's disease, Parkinson's disease, and Huntington's disease (APHD) are regarded as the three major neurodegenerative diseases. There is a vast body of literature on the causes and treatments of these neurodegenerative diseases. However, the main obstacle in developing an effective treatment strategy is the permeability of the treatment components to the blood-brain barrier (BBB). Several strategies have been developed to improve this obstruction. For example, nanomaterials facilitate drug delivery to the BBB due to their size. They have been used widely in nanomedicine and as nanoprobes for diagnosis purposes among others in neuroscience. Nanomaterials in different forms, such as nanoparticles, nanoemulsions, solid lipid nanoparticles (SLN), and liposomes, have been used to treat the neurodegenerative diseases. This review will cover the basic concepts and applications of nanomaterials in the therapy of APHD.

Key words: Neurodegenerative diseases; Blood-brain barrier; Drug delivery; Nanocarriers

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1. Introduction

Neurodegenerative diseases refer to the malfunctions of the CNS commonly caused by neuronal dysfunction and death. Major neurodegenerative diseases include APHD (Figure 1). Alzheimer's disease, which is the most prevalent neurodegenerative disease, is the formation of amyloid plaques and neurofibrillary tangles by neuro-inflammation. Another indication of the disease is a drop in the levels of the neurotransmitter acetylcholine.(1) Mostly, Acetylcholine esterase inhibitors (Rivastigmine, Donepezil, and Galantamine) and Memantine are administered as the conventional Alzheimer's disease treatment.(2) The second most common neurodegenerative disease is Parkinson's disease, which typically features a reduced number of dopamine-producing neurons and the presence of Lewy bodies. After the appearance of the initial symptoms of Parkinson's disease, 80% of the dopaminergic neurons become destroyed in the substantia nigra. Typical symptoms include rigidity of the body, tremors, slow body movements and difficulty in walking. Currently, the disease remains incurable and only few symptoms can be treated.(3) Levodopa and dopamine agonists are considered as the main treatment for the Parkinson's disease.(4) Another common neurodegenerative disease is known as Huntington's disease, which is an inherited, autosomal dominant disease that results in jerky movements or chorea, dystonia, incoordination, and behavioral changes. Huntington's disease remains incurable and currently only symptomatic treatments exist.(5) Antidopaminergic agents such as Tetrabenazine are the main pharmaceutical options for the Huntington's therapy.(6)

New therapeutic approaches need to manage these neurodegenerative diseases because the current therapies are limited in many areas.(7-10) The BBB , which is the main obstacle met when treating diseases of the CNS, is composed of endothelial cells forming tight junctions and separates blood from the extracellular fluid of the brain. Furthermore, the permeability of the BBB is selective for only certain substances such as nutrients and water. Thus, the barrier prevents the passage of certain drugs and therapeutic agents required for the treatment of the disorders related to the CNS.

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The need for new therapeutic approaches of neurodegenerative diseases and the limitations caused by the BBB are advancing the use of nanotechnology to establish targeted drug delivery to the CNS. Nanotechnology is a field that is developing at a fast pace with respect to its applications in medicine.(11-19) Nanomaterials can be highly suitable drug carriers to the brain owing to their physical and chemical properties. When manipulated in the right way, nanocarriers can efficiently overcome the BBB.(20)

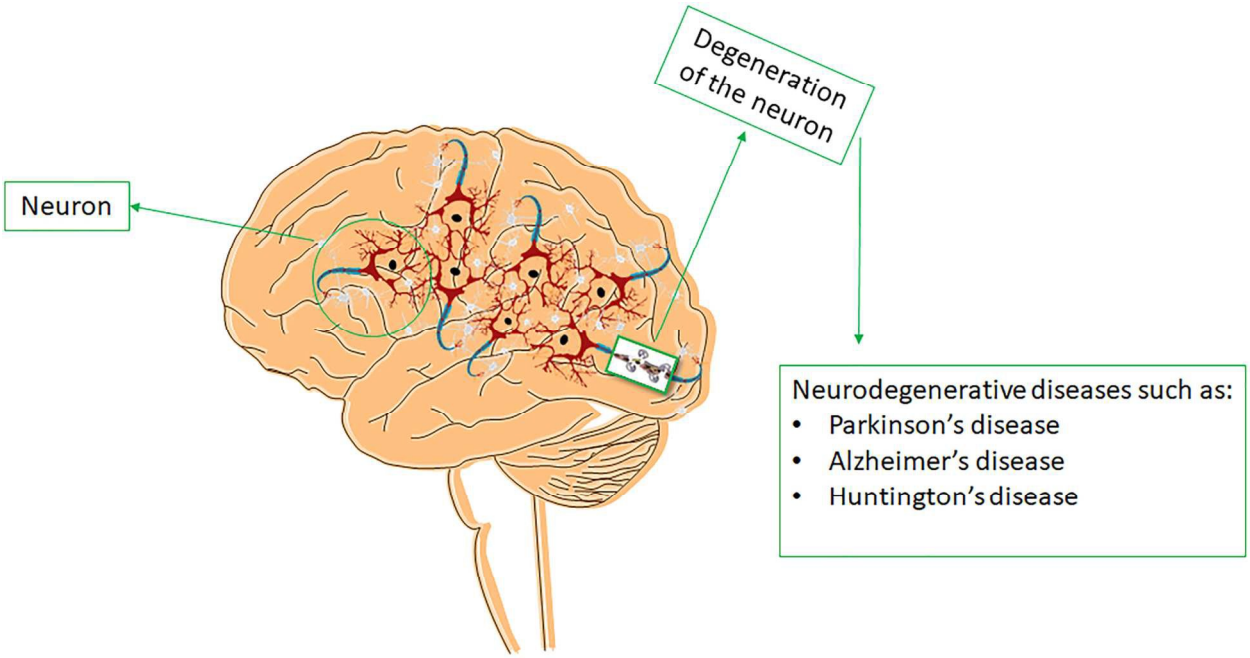

Figure 1 Overall scope of neurodegenerative diseases

Nanoparticles have gained wide interest due to their characteristics including high capacity for drug loading, lower or no systematic toxicity, physical and chemical stability, pharmaceutical improvement of drug properties, and drug permeabilization.(21-27) However, the penetration of the nanoparticles through the BBB highly depends on the type, size, surface chemistry, and polarity of the particles.(28) This review discusses the application of drug-loaded nanocarriers in the treatment of neurodegenerative diseases.(7)

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2. Neurodegenerative diseases

Diseases of the brain can be divided into three main classes, namely the neurodegenerative diseases, neuroinflammatory diseases, and neoplastic diseases.(29) Neurodegenerative disorders includes different types of conditions which are either sporadic or familial or both and their common cause is the continual loss of neuronal subtypes.(30) APHD are known as the most common neurodegenerative diseases. For example, Alzheimer's disease was the cause of dementia in 60% of around 24 million people suffering from this disorder in 2005.(31)

Many studies have reported the impact of neurodegenerative diseases on the BBBs, most plausibly through neuro-inflammation.(32) Changes to the BBB not only prevent it from performing its normal functions, such as transporting nutrients, its role as a signaling interface, enhancing immune cell entry, and maintaining homeostasis, but also hinder the transport of drugs to the CNS to manage neurodegeneration. The adopted notion is that the BBB is a static element, i.e., immune to brain changes. However, it is likely that the BBB undergoes changes in the case of neurodegeneration, which can be interpreted in three different ways: (1) the changes in the BBB may be the consequence of the disease; (2) BBB changes account for the disease; or (3) BBB changes participate in the disease pathogenesis. Based on evidence from previous findings, the BBB may be involved in the initial degenerative process in patients suffering from neurodegenerative diseases. Furthermore, most reports have demonstrated that the pathogenic process plays also a role in the dysfunction of the BBB.(33)

The exact factors that cause neurodegenerative diseases are still unknown. A family history of neurodegenerative diseases increases the risk of developing the disease, which indicates a genetic component in the initiation of neurodegeneration. Moreover, the risk of developing a neurodegenerative disorder increases with advanced age. Programmed cell death or apoptosis is another known cause for neurodegeneration, which is especially observed in Parkinson's diseases.(29)

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Neurodegenerative diseases are often associated with neuronal loss and cell death. The neurons that survive exhibit changes in nuclear defragmentation, size, shape, chromatin condensation among other morphological changes.(29) Neurodegeneration occurs when neurons cannot terminate the apoptotic phase due, thus becoming inflamed and necrotic.(34) Different neurodegenerative diseases will be discussed in the following paragraphs.

2.1 Alzheimer's disease

Alzheimer's disease is considered the most common neurodegenerative disease. Currently, there is no cure available to treat Alzheimer's disease, and therapeutic interventions are aimed at managing, i.e., mitigating or halting, the associated symptoms. Almost 1% of the population between the ages of 50 to 70 years suffer from Alzheimer's disease, and the percentage affected increases to 50% beyond the age of 70 years.(20) The primary clinical symptoms detected in patients with Alzheimer's disease include dementia, along with impaired learning and cognition.(29) Later stages of the disease are accompanied by increased irritability, confusion and behavioral changes.(30, 35) One particular feature observed in the brain of Alzheimer's disease patient is the presence of a unique pattern of beta-amyloid plaques and neurofibrillary tangles. As a result of weakened metabolism of the amyloid precursor protein, beta-amyloid plaques are formed. It is the aggregation of these plaques that is responsible for the neuronal damage. Diffusible ligands and oligomers derived from toxic beta-amyloid plaques contribute directly to the neurotoxicity associated with Alzheimer's disease.(36, 37) The extent of beta-amyloid plaques deposition and its location has been directly associated with the amount of neuronal damage and the ensuing dementia after diagnosis .(38) Neurofibrillary tangles are paired helical filaments of microtubule-associated tau protein that supports neuronal growth under physiological conditions, but becomes cytotoxic when hyperphosphorylated.

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With the progress of Alzheimer's disease, loss of cholinergic neurons has been specifically observed, indicating that the acetylcholine neurotransmitter is involved in the areas of memory and cognition in the brain.(39) Alzheimer's disease currently has Various treatment options including Donepezil, rivastigmine, and galantamine that are frequently prescribed drugs to improve the bioavailability of acetylcholine by preventing its breakdown. In addition, currently available drugs included acetylcholine esterase inhibitors, which prevent acetylcholine breakdown.(40) Other treatment options that have been proposed are the use of anti-inflammatory drugs and antioxidants such as α-tocopherol and non-steroidal anti-inflammatory medications.(41) Some researchers have shown that immunotherapy can be used for the solubilization of beta-amyloid plaques. The future of Alzheimer's disease treatment lies in focusing on preventing beta-amyloid plaque formation or supporting their clearance. Solubilization of beta-amyloid plaque has also been successfully induced by humanized monoclonal antibodies such as bapineuzumab and solanezumab.(42)

2.2 Parkinson's disease

Another major neurodegenerative brain disorder that affects a large population is Parkinson's disease, which affects 1% of the population of 65 years or older.(20) Pathologically, the loss of dopaminergic neurons in the substantia nigra pars compacta causes Parkinson's disease.(43) The major disease symptoms are caused by dopaminergic deficiency in the striatum and include tremors, hypokinesia, diminished balance, and rigidity of the body. The main feature of Parkinson's disease is the presence of intracellular eosinophilic inclusions called Lewy bodies, which are abnormal protein aggregates. Furthermore, the loss of striatal dopaminergic neurons, which are responsible for motor coordination, are the main cause of the disease symptoms.(44) Similarly to Alzheimer's disease, the exact cause of Parkinson's disease is still unclear. Changes in the CNS associated with Parkinson's disease include protein aggregation, neuroinflammation, oxidative stress, mitochondrial dysfunction,

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and damages to the BBB integrity. When the parkin and synuclein genes are mutated, the function of the ubiquitin-proteasome pathway, which is responsible for the clearance of aggregated and excessive proteins, becomes altered. As a result, abnormal proteins aggregate, thus ensuing neuronal death.(45) Another theory put forward regarding the mechanism of Parkinson's disease is related to mitochondrial dysfunction. Indeed, aging and toxins accumulation jeopardize the energy resources provided by mitochondria. As a result, mitochondrial functioning is adversely affected and the energy required by the neurons is not received, thus leading to synuclein production in Parkinson's disease, which causes neuronal damage.(29)

Currently, only symptomatic therapies are available for patients with Parkinson's disease, i.e. relieving or preventing the associated symptoms, involving the increase of the dopamine action period and mirroring dopaminergic actions. Several dopaminergic agonists are available and used for Parkinson's disease treatment.(29) For example, levodopa acts as a dopaminergic agonist and carbidopa prevents metabolism at the periphery; when used together, both have the same action as dopamine. When administered orally, the pace of levodopa decarboxylation is very high; thus, by the time the drug enters the CNS, only a small amount remains unmodified. Therefore, in order to maintain its effectiveness, the levodopa dosage should be high enough to enable a substantial unmodified amount to reach the CNS. However, increasing the dose is associated with possible side effects, such as depression, anxiety, insomnia, agitation, nausea, and vomiting.(3)

2.3 Huntington's disease

Huntington's disease is a genetic neurodegenerative disease that affects the cognitive and motor abilities, with a prevalence of five to seven in every 100,000 people.(5) Similarly to other neurodegenerative diseases, Huntington's disease is associated with a decline in cognitive skills. Other common symptoms of the disease are mood swings, psychosis, inability to empathize, inability to

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maintain relationships, and becoming self-centered. The most characteristic physical symptoms of Huntington's disease are random and uncontrollable movements called chorea. Many of the symptoms observed at the onset of Huntington's disease are similar to those of Schizophrenia, particularly the lack of social cognition.(46) Broadly, the disease can be divided into a pre-diagnostic and a diagnostic stage. During the pre-diagnostic stage, the changes that occur, involving alterations in personality, cognition and motor control(47) may remain unnoticed by the patient and family members. This stage is followed by the diagnostic stage during which patients suffer from incoordination, chorea, motor impersistence, and slowed saccadic eye movements.(5, 48)

Studies reporting on symptomatic and protective treatments have been previously performed. Symptomatic treatment includes treating unusual movements, cognitive impairment, and psychiatric symptoms. In the case of Huntington's disease, tetrabenazine (TBZ) is currently the only drug approved by the Food and Drug Administration (FDA) for the symptomatic treatment in Huntington's disease. Vesicular monoamine transporter 2 concentrates monoamines into the vesicles, while TBZ reversibly inhibits this action, thus resulting in a more enhanced reduction of presynaptic dopamine than serotonin and norepinephrine.(6, 49, 50) The causes, symptoms, and conventional treatments of all three neurodegenerative diseases are summarized in Figure 2.

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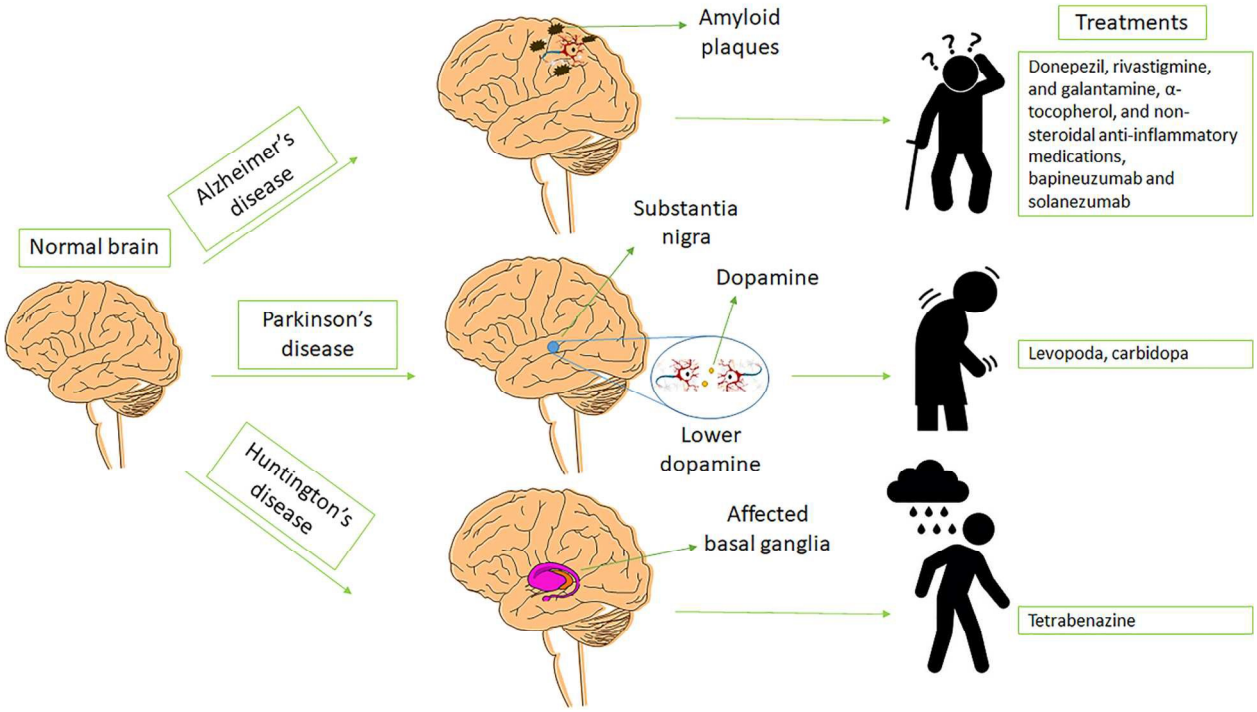

Figure 2 Causes, symptoms, and general treatments of neurodegenerative diseases

3. BBB

3.1 Structure

The BBB is a specialized endothelial cell lining the intraluminal part of the brain capillaries, and splits the peripheral circulation from the CNS. The BBB is present to maintain a constant internal environment of the brain. Astrocytes, neurons, pericytes, and extracellular matrix are the other components of the BBB (Figure 3).(51) Polar solute movement is prevented across the cerebral endothelium due to the lack of aqueous pathways and tight continuous circumferential junctions present between cells.(52) The BBB enables the brain to maintain homeostasis and an unchanging environment while protecting the underlying brain cells. It also protects the brain from the entry of potentially toxic substances. Even during early development of newborns, the BBB provides the brain with a particular internal environment that helps neurons connect and grow.(53) However, the brain is

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not totally inaccessible because of the barrier(54), and endothelial cells use several specific transport systems to enable the access of ample amounts of nutrients across the BBB.(52)

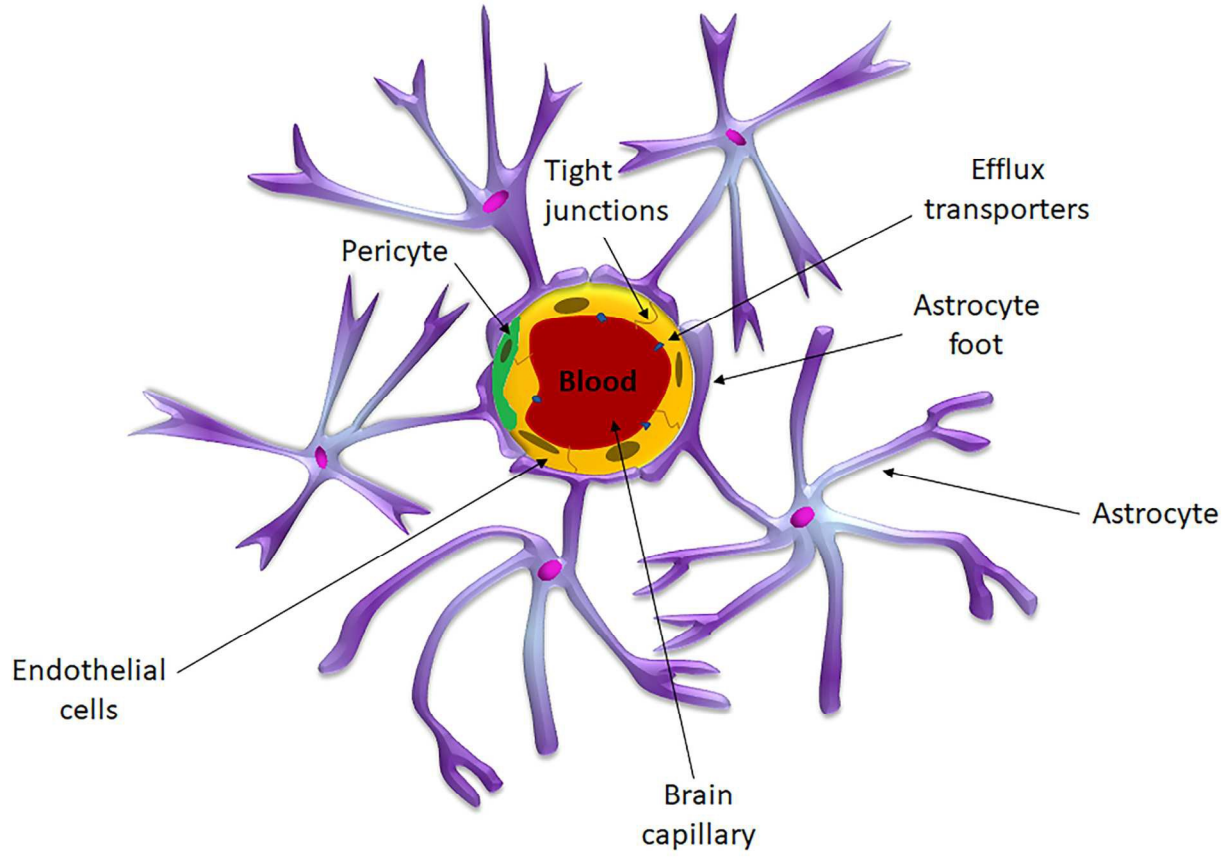

Figure 3 Capillary structures of the BBB

Our understanding of the BBB and how it functions have significantly improved after researchers have studied it on a cellular, metabolic, kinetic, and molecular level. Substances that may be toxic to the brain must be excluded from it and eliminated via the blood. This process is also dependent on the BBB mechanisms. The luminal surface of the capillary endothelial cells contain P-glycoprotein, which acts as an efflux pump and restricts cytotoxic drugs from accumulating.(55) Carrier mediated transport is the mechanism by which nutrients are supplied to the brain via the capillary endothelial luminal and the abluminal membranes.(56) The abluminal membrane of the endothelial cells is in connection with the

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brain extracellular fluid, while the luminal membrane of the endothelial cells is with the blood component.(55) Glucose is transported to the brain with the help of a facilitated carrier of endothelial cells known as glucose transporter 1 (GLUT-1).(57) There are several transporters present to get amino acids across the BBB. System-L, an energy dependent transporter, transports valine, histidine, methionine, tyrosine, and phenylalanine to the brain, and can be found on both the luminal and abluminal membranes. Few neutral amino acids, namely alanine, serine, and cysteine, are transported by the Alanine/serine/cysteine (ASC) transporter. Figure 4 illustrates the main transport systems that facilitate the movement across the BBB.

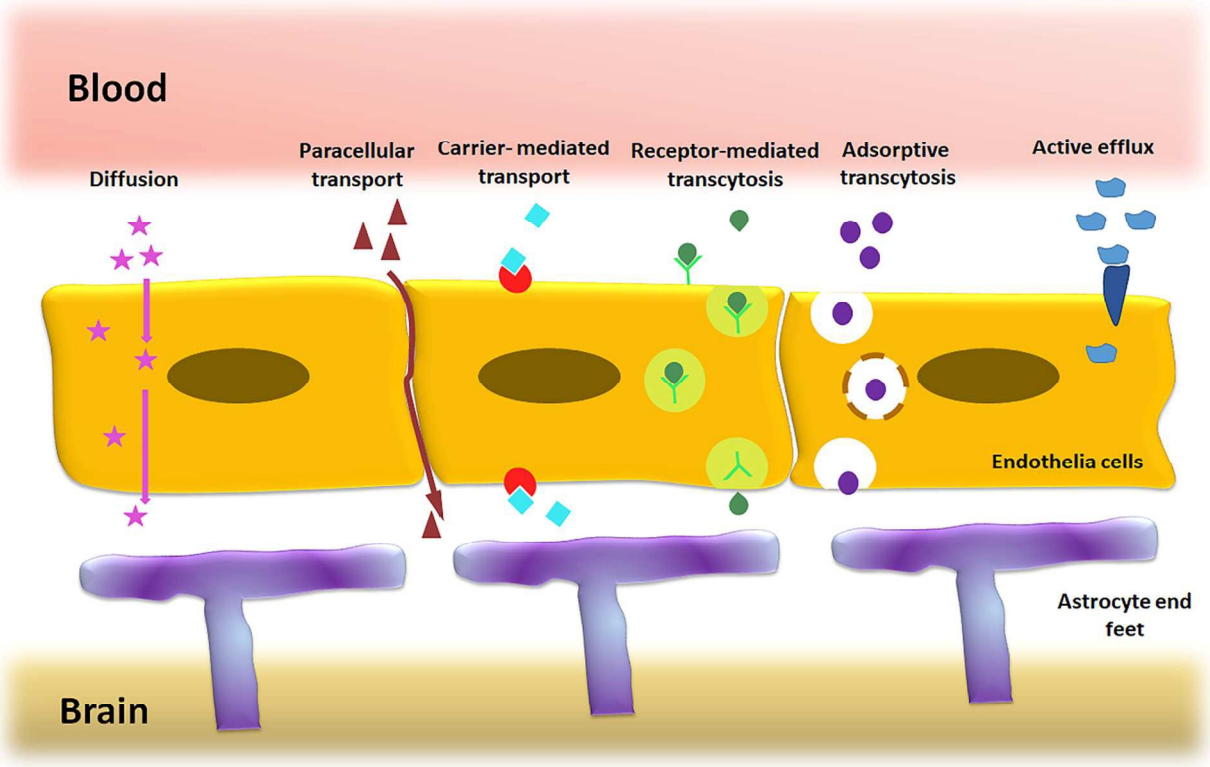

Figure 4 Transport pathways of endothelial cells in the BBB

BBB defects can cause brain edema, auto-immunity, and several other disorders of the human body.(58) Several methods to overcome the BBB have been investigated and include the use of

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antibodies,(59) liposomes,(60) nanoparticles, chimeric peptides, biochemical opening,(61) and osmotic opening of tight junctions, thus, strategically facilitating the brain drug delivery.(62, 63)

3.2 Drug Passage across the BBB

The BBB prevents the transport of all molecules except the ones that are small enough in size. This becomes a major problem for the treatment of brain disorders such as APHD, and brain cancers. Agents that are difficult to transport across the BBB include CNS active drugs, such as antineoplastic agents, neuropeptides, and antibiotics. Specialized transport systems are generally required even for the uptake of molecules that are relatively small such as amino acids and glucose by the brain.(58) The BBB is a part of the human body that remains least accessible to active pharmacological molecules. Although effective for the treatment of neurodegenerative diseases, conventional methods are much below the levels of optimum efficacy. Therefore, there is a need to develop therapeutic alternatives.(29)

The endothelial cells of the BBB are equipped with lipophilic membranes. Thus, substances that must pass into the CNS must move from the hydrophilic environment of the blood to the hydrophobic environment of the endothelial cells. In addition, drugs can pass through small pores that are filled with water or through the cellular channels. Molecular size, drug lipophilicity, drug ionization, and plasma protein binding are drug properties that influence this process.(64) Studies have shown that lipid-soluble molecules with a low molecular weight around 400–600 Da are generally transported across the BBB.(65)

Free drugs can be delivered through the BBB by different methods including physiologically based, pharmacologically based, and invasive methods.(66) Invasive methods include BBB disruption, intra-ventricular drug infusion, and cerebral implants. Disruption of the BBB can be induced by osmotic or biochemical means. Intra-cerebral implants can alter the BBB permeability.(65) Osmotic BBB opening or

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the application of biologically active agents such as bradykinin and histamine are other widely used techniques.

4. Facilitated drug delivery through the BBB

Disorders of the brain that are caused by the absence of peptides or hormones can be treated by administering those elements in a controlled manner. Controlled administration is an approach that can be used to treat common neurodegenerative disorders. However, for oral administration, there are very few stable small molecules that can act on neurons. The problem lies in the fact that proteolytic enzymes can easily degrade peptide drugs and result in the inaccessibility of the drugs to the site of action.(44) To overcome these problems, different methods are used to help the drug delivery across the BBB. More details are discussed below.

4.1 Lipidization

Lipidization of a molecule by surrounding it with a layer of lipids can improve the lipophilicity of a hydrophilic substance, which in turn improves its chances of penetrating the BBB. A hydrogen bond forming a polar functional group can be replaced by an apolar functional group, which does not form any hydrogen bonds with water. Codeine and heroin formation by O-methylation and O-acetylation of morphine, respectively, are classical lipidization techniques. When two hydrogen bonds are removed during the formation of codeine or O-methylation of morphine, the permeability of the BBB increases by ten folds of its baseline value.(67) It would be an extra advantage if the lipidization process is reversible and is converted back to the original molecule once the drug reaches the brain.(65) Paying attention to the efflux mechanisms of the drugs is of great importance. With respect to morphine, the brain-to-blood efflux rate is at the same slow pace as the blood-to-brain entry. The retention time, required for the conversion of the pro-drug to the drug, enables the retention of the drug in the brain. Lipidization can also be attained by the formation of fatty acids or cholesterol following the attachment of free fatty acyl

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or cholesterol esters. Intravenous injections of these drugs exhibit better passage across the BBB, but may not be successful if administered orally.(68) The reason is that once fatty acyl or cholesterol esters is absorbed orally, it merges into lipoproteins resulting in a reduction in the ability to cross the BBB in comparison to free cholesterol.

4.2 Disruption of the BBB

Disruption of the BBB is another method by which molecules can cross the barrier. Some causes of disruption include hypertension, CNS tumors, seizures, and exposure to radiation.(55) The objective of disrupting the barrier is to either create a para-cellular transportation route across the endothelium or to create a trans-cellular pathway through the endothelium. Infusion of a hypertonic solution can disrupt the BBB. This can also be induced using angiotensin, bradykinin, or other biologically active agents that might be involved in controlling the behavior of the BBB.(55)

As mentioned above, osmotic opening is one of the most common techniques used to pass through the BBB. Mannitol is usually the hypertonic solution that is infused into the carotid artery. By this method, large molecules can enter the CNS. One reason why this works may be because the para-cellular pathways are physically opened due to the endothelial cells shrinking when in contact with the osmotic agent.(52) Osmotic disruption along with the infusion of drugs has been helpful in the treatment disorders related to the CNS such as brain cancer. Patients who received this treatment did not show any significant side effects and demonstrated an improvement in their survival time.(69) The only problem associated with this procedure is the inability to predict the long term neurological effects on the brain. Few cases were reported to have seizures following this procedure.(70)

Radiation has been known as a cancer therapy method. More than that, it can disrupt BBB and facilitate the agent delivery to the brain.(71) It was shown that radiation can change the tight junction structure that results in the higher size dependent permeability of BBB both paracellularly and

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transcellularly.(72) BBB disruption with 60 Gy radiation has been confirmed.(73) The brain necrosis or delayed necrosis after months or years are considered as the major shortcoming of radiation. To solve for this problem scientists tried to optimize the dosage of radiation.(74) Reinhold believed that the optimal dose of 20 to 25 Gy radiation leads to more diffusion alterations.(75)

Focused ultrasound (FUS) is another method that can noninvasively help drug delivery to BBB.(76) Ultrasound can locally and selectively disrupt BBB with considerable damage to the brain tissue.(77) A circulating agent containing gas bubbles has been added to FUS that makes the BBB disruption reversible.(78) One of the major disadvantages of this method is the ultrasound attenuation by bone tissue of the skull followed by a wave distortion. Thus, an acoustic window should be designed using craniotomy.(77) To overcome this problem, FUS has been combined with imaging technologies like CT scans, MR imaging (MRI), and MR temperature imaging (MRTI) to control the heating and wave distortion related to FUS prevent craniotomy.(79, 80)

4.3 Penetrating the BBB via nanomaterials

Nanomaterials are materials with dimensions between a few to a hundred nanometers. The role of nanomaterials in medicine today is immense because their particle size is comparable to the size of proteins, nucleic acid, and antibodies. They also have a surface-to-mass ratio that is much higher than that of other particles. These biomimetic features together with their quantum properties, ability to carry and absorb other substances, and biodegradability make nanomaterials the most potent tools in modern medicine.(81) In neuroscience, the interaction with neurons at a molecular level is regarded as one of the main roles of nanomaterials. They also can be used to overcome the biggest obstacle in delivering drugs to the brain caused by the BBB.(82) Ideally, nanomaterials containing drugs are administered systemically to the patient, enabling them to cross the BBB and release drugs into the brain cells. This procedure could be very challenging and multidisciplinary solutions from different fields

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such as engineering, medicine, chemistry, nanotechnology, pharmacology, and physiology are required.(83) With the advances in these areas, nanomaterials are not only used to serve as vectors to transport drugs across the BBB but researchers are also looking at multifunctional nanoparticles to help in the detection, treatment, and monitoring of brain diseases.(84) The application of nanotechnology to the field of medicine and health care is known as nanomedicine. Nanomedicine has the potential of significantly improving and changing the face of drug delivery, medical imaging, tissue regeneration, faster diagnoses, and other medical treatments.(85) There is a significantly lower amount of risks involved in using nanomaterials when compared to conventional methods used to treat brain diseases. Biodegradability and reduced toxicity to peripheral organs are added advantages of using nanomaterials for therapeutic purposes.(86)

Penetration of drugs into the brain via nanocarriers can be achieved through different delivery systems such as carrier-mediated transport, chemical drug delivery systems, receptor mediated transport, active drug delivery systems, and endocytosis.(87) Loading nanoparticles with drugs can be done by different methods including covalent linkage, encapsulation, and adsorption.(88-90) Nanomaterials are considered the future of brain drug delivery to tackle neurodegenerative diseases because they are comparatively less toxic, more biocompatible, stable, biodegradable, and have the potency of drug delivery to the CNS by crossing the BBB.(91)

Nanomaterial drug delivery systems are not only used as the treatment of neurodegenerative diseases and brain cancers but also for a better brain delivery of antiretroviral drugs, which are required for the treatment of patients infected with the human immunodeficiency virus. During the early stages of the infection, the virus enters the CNS. As a result, an independent viral reservoir is formed after being able to replicate actively in the brain compartment, thus causing drug resistance, complications, and infection. Several antiretroviral drugs available today are unable to overcome the BBB. Previous

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studies have demonstrated that the concentration of the drug in the brain could be significantly elevated with the help of liposomes, SLN, micelles, and polymeric nanoparticles. Thus, the human immunodeficiency virus loaded in the brain could be significantly reduced by increasing the bioavailability of antiretroviral drugs through nanomaterial drug delivery systems.(92)

Nanomaterial drug delivery systems can spare healthy cells by modifying nanomaterials to target diseased or abnormal cells selectively. In one particular study, a group of researchers used polylactic co-glycolic acid (PEG)-coated hexadecyl cyanoacrylate nanoparticles to encapsulate an antineoplastic drug against glioma.(93) This method was proposed as an alternative for chemotherapy. Authors used spectroscopy, atomic mass microscopy, and other physical and chemical characterization methods to prove that the drug was efficiently loaded onto the nanoparticles. They also demonstrated the control of the drug release kinetics into the cells. Moreover, PEG-coated nanoparticles exhibited higher accumulation and diffusion/convection through the leaky BBB and a higher affinity to the normal BBB compared with the control sample due to its long circulating properties in Fischer rats bearing gliosarcoma.(93) In another study, rats were injected systemically with superparamagnetic SLN, which were made from microemulsions of solidified oil nanodroplets containing iron oxide and used as detection agents for MRI contrast.(94) After injection, the lipid nanoparticles exhibited a slower clearance and gathered in the brain after overcoming the BBB.(94)

The exact mechanism by which nanomaterials can cross the BBB is not fully understood. However, several possibilities have been suggested. The most probable mechanism may be through endocytosis by endothelial cells that line the brain capillaries. Once the particles are taken up by the endothelial cells, they are released inside the brain possibly through transcytosis. Tight junction modulation or P-glycoprotein inhibition may be the other processes by which nanomaterials cross the BBB. Furthermore, it is plausible that these processes occur in parallel.(95)

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Surface modification is another method to enable drug-loaded nanoparticles to overcome the BBB. Surface modification can be induced by conjugating the drug-loaded nanoparticles with antibodies that are specific to the brain. Subsequently, the specific ligand recognizes the conjugate and allows the nanoparticles to pass through the BBB. However, the biggest hurdle here lies in the fact that it is very difficult to find specific ligands for the target tissue.(96) Specificity can also be achieved by coating the loaded nanoparticles with different surfactants.(95, 97) The ability for a surfactant to be efficient at targeting depends on its physicochemical and biochemical properties. Poloxamer 188 (F68) is one such surfactant that can improve the permeability of drug-loaded nanoparticles to the brain significantly. For example, it was obtained that Poloxamer 188 can enhance drug delivery of polybutylcyanoacrylate and poly(lactide-co-glycolide) (PLGA) nanoparticles loaded with drugs into the rat brain.(98, 99)

Figure 5 illustrates the different types of nanomaterials that have been used to treat neurodegenerative diseases.

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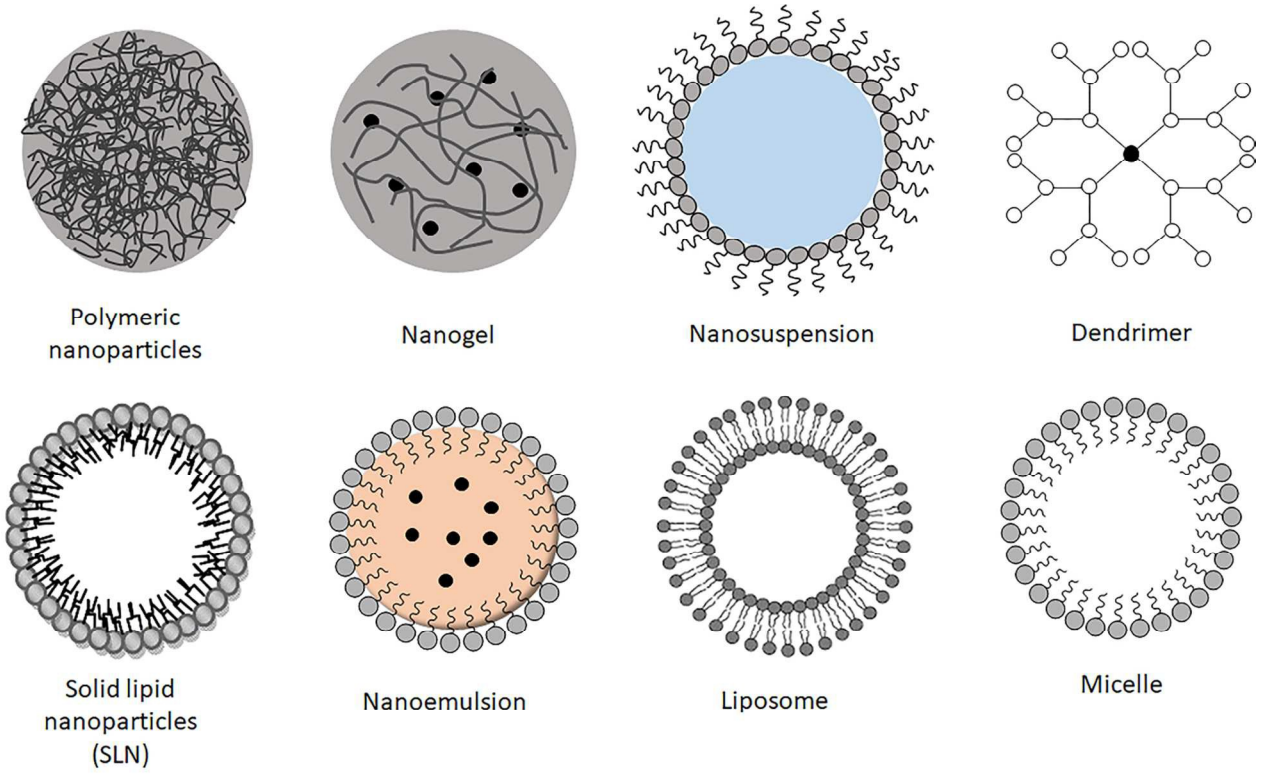

Figure 5 Available forms of nanoparticles that are used in the treatment of neurodegenerative diseases

4.3.1 Nanoparticles

Polymeric nanoparticles have been intensively investigated in medicine because of their biocompatibility, biodegradation, and low toxicity.(100-102) However, one obstacle in utilizing polymeric nanoparticles for drug delivery is engineering them into target-specific and stable systems. The role of the drug delivery system with respect to targeting does not end once it has entered the brain; it needs to have the ability to release the drug selectively to tissues or cells that are affected by the neurodegenerative disorder.(103) To date, only a few cases of polymeric nanoparticles using selective strategies have succeeded clinically.(104)

One of the most commonly used polymeric nanoparticles in nanomedicine is PLGA,(105, 106) which has been approved by the FDA and the European Medicine Agency (EMA). It is well known for its high

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biodegradability, which is essential in drug delivery systems. Yadav et al. studied the effect of PLGA nanoparticle size on biodistribution and blood clearance.(107) They used PLGA nanoparticles loaded with etoposide, and the size of the nanoparticles ranged between 100 nm and 160 nm. The results showed that for long-term circulation without any surface modification, the 100 nm nanoparticles worked best because they could escape the liver metabolism.(107) This and several other studies suggest that PLGA is a promising candidate for enhancing therapeutic delivery into the CNS.(108-120)

However, PLGA degrades by bulk erosion, which can lead to premature exposure of the therapeutic to a degradative environment.(121) Additionally, the therapeutic release profile of PLGA nanoparticles is difficult to control due to the penetration of water into the bulk.(122) These issues could potentially be solved using surface-eroding polyanhydride nanoparticles. Also FDA-approved, these nanoparticles are biocompatible and induce low inflammatory responses in vivo.(123-129) Because they erode from the surface, the release timescale can be precisely tuned by altering the nanoparticle chemistry to deliver therapeutics at the right time and therefore enhance therapeutic efficacy while also lowering the effective dose.(130-132) Importantly, they are also small enough, around 300-400 nm, to be efficiently internalized by many different cell types.(133-135) Overall, polymeric nanoparticles are the most preferred nanocarriers as they are easy to fabricate, stable, safe, and exhibit better controlled release of drugs. However, one of the biggest challenges for the therapeutic use of polymeric nanoparticles is the scale-up procedure keeping in mind the cost factor.(109)

4.3.2 Nanogels and nanosuspensions

Polymers that form crosslinked networks are able to combine ionic and nonionic polymeric chains to form nanogels.(21, 136) Natural polymeric materials have been broadly applied in tissue engineering and drug delivery.(137-145) Nanogels have the ability to carry oligonucleotides, DNA, proteins, low molecular weight drugs, and other small molecules after swelling up in water. Vinogradove et al. studied

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the passage of crosslinked nanogels encapsulating oligonucleotides across the BBB *in vivo*.(20, 146) Their results indicated that the uptake of nanogel in the spleen and liver was decreased, while it was increased in the brain.(20, 146) Nanosuspensions are another type of nanomaterials that can be potentially used for delivering molecules across the BBB. They can carry drug particles that are crystalline in nature and stabilized by nonionic surfactants or lipid mixtures.(147) Nanosuspensions are known for their good drug loading capacity and simplicity. Thus, they can be potentially used to deliver several drugs across the BBB to the CNS.(20, 147, 148)

4.3.3 Dendrimers

Dendrimers are nanoscaled macromolecules that have repetitive branching.(149) The functional groups at the exterior of dendrimers are largely responsible for trapping drug molecules to be transported into the brain.(150) Dendrimers can be used to overcome the difficulties that other drug delivery systems experience for brain delivery, such as bad permeability across the BBB, resistance development to drugs, and limited selectivity to diseased cells. Dendrimers can be used to target the brain, which can be achieved because of their structure, small nanometric size range, and functional advantages. Dendrimers have many surface groups that can be exploited and used to conjugate multifunctional ligands. Another advantage is that drugs can be entrapped in the spaces present in dendrimers, thus enabling the protection of the drugs from the external environment.(151)

The passage of polyether-copolyester dendrimers crossing the BBB has been studied previously by labeling dendrimers with rhodamine B. At high concentrations, the brain vascular endothelial cells were saturated with the polyether-copolyester dendrimers. Furthermore, the dendrimers were inhibited fractionally by clathrin and caveolin. Their results highlighted the influence of the architecture of dendrimers on the crossing of the BBB.(150, 151)

4.3.4 Solid lipid nanoparticles (SLN)

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Many lipid-based nanocarriers have been investigated and proved to have great potential in drug delivery to the brain. These lipid-based nanomaterials are both biocompatible and biodegradable. Lipophilic materials work very well at targeting and crossing the BBB.(92) Compared to other nanocarriers, SLN are relatively new (Figure 6A,B),(152, 153) stable, and can be produced by multiple methods such as solvent injection, microemulsification, solvent emulsification, and high pressure homogenization. They are essentially comprised of an aqueous surfactant that includes dispersed melted lipid.(150) The target drug to be transported to the brain is usually present in the hydrophobic core of the SLN.(154) Furthermore, drug release from these nanoparticles can be controlled and can last for months due to their excellent drug entrapment ability and stability (Figure 6C).(155)

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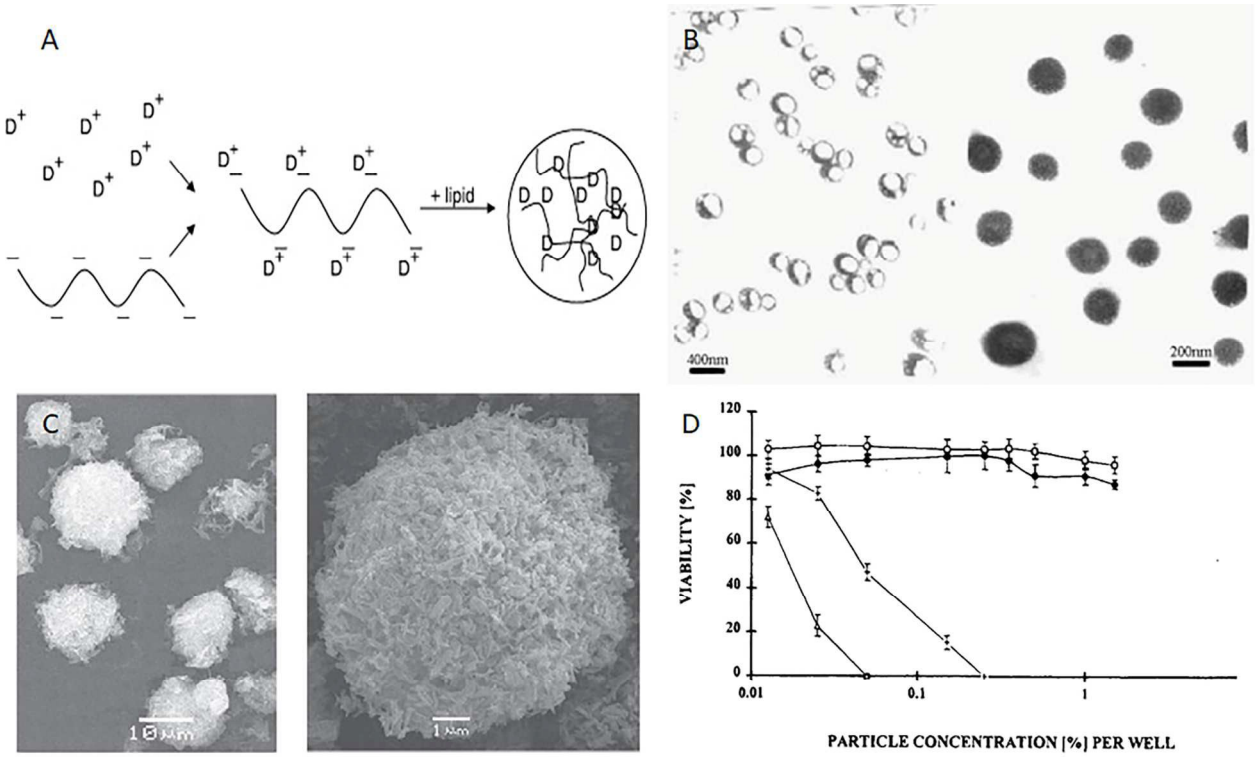

Figure 6 (A) polymer-lipid nanoparticle (PLN) formation. D^+ represents the water-soluble cationic drug molecule and curved line shows the anionic polymer chain. The charges of the two molecule are neutralized and results in the PLN formation.(152) (B) Transmission electron microscopy (TEM) of blank Solid lipid nanoparticles (SLN) and Actarit-loaded SLN (right).(153) (C) Scanning electron microscopy (SEM) of dry powder inhalation (DPI) system of SLN loaded with insulin.(155) (D) Cytotoxicity comparison of the Dynasan-SLN (□), Compritol-SLN (●), polyhexylcyanoacrylate (+), and polymethylcyanoacrylate (Δ) nanoparticles in contact with human promyelotic HL60 cell lines. Cells showed higher viability exposed to SLN nanoparticles compared to the reference drug carriers.(156)

The boiling points of SLN are a little higher than the body temperature; hence, once these nanoparticles enter the body, they turn into solid particles. It has been previously demonstrated that SLN exhibit low non-specific cell toxicity (Figure 6D).(156) In a lipophilic environment, SLN become immobilized, which protects them from degradation. In another study, SLN loaded with nitrendipine as the target drug were fabricated using triglycerides, emulsifiers, and charge modifiers.(157) Compared to the nitrendipine suspension, which presented an elevated drug concentration in the brain over 3 h, the nitrendipine-loaded SLN presented a high drug concentration for double the amount of time.(157) Thus, SLN present a possible drug delivery system to treat neurodegenerative diseases.(150)

4.3.5 Nanoemulsions

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The dimensions of nanoemulsions range between 20–200 nm (Figure 7A).(158) This oil in water formulation consists of an oil phase in dispersed droplets, and also has surfactants and co-surfactants that stabilize it. Nanoemulsions are especially suitable for highly lipophilic drugs that need to be transported to the brain,(92) and can be prepared either by high or low energy methods. The oil component of a nanoemulsion is of great importance in the brain drug delivery process. nanoemulsions have been proven to have selectivity in uptake of needed polyunsaturated and omega-6 fatty acids, pinolenic acid, and linoleinic acid.(150) Edmond et al. demonstrated that oleic acid, which has one cis-double bond, was not transported across the BBB, while linoleic acid, having two cis-double bonds and 18 monocarboxylic acids, was successfully transported to the brain.(159) Therefore, there is a lot of therapeutic potential in this type of lipid nanocarriers.

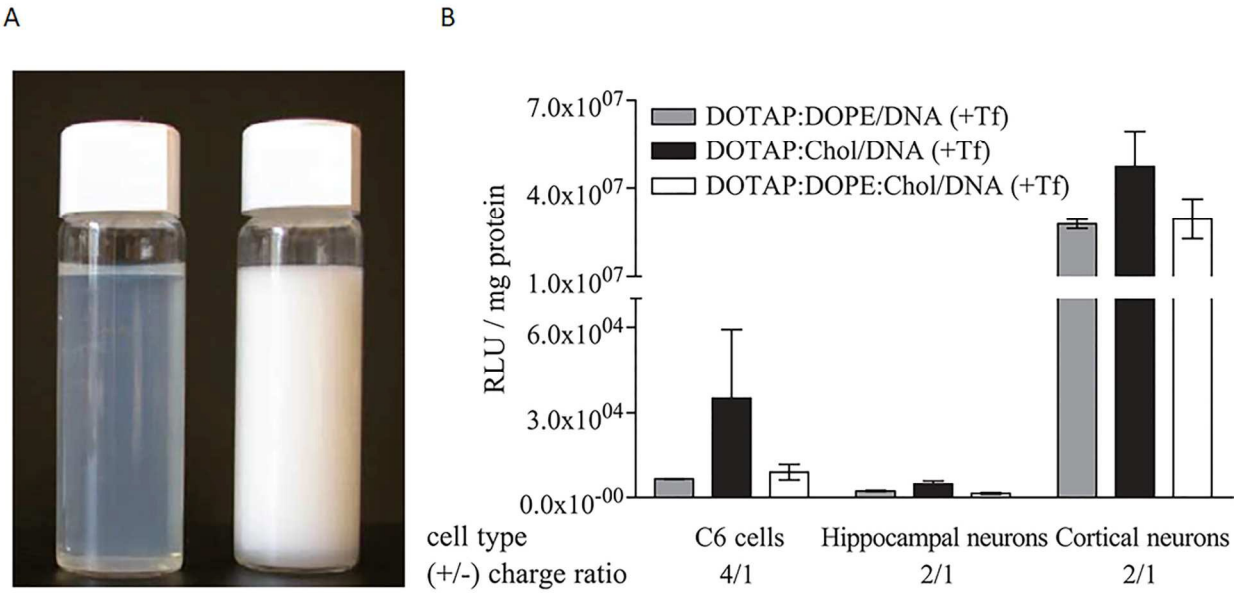

Figure 7 (A) Nanoemulsion (left) and Macroemulsion (right).(158) (B) The effect of liposome composition on cell transfection. Cholesterol in a cationic liposome formulation, such as DOTAP, acts as a helper lipid to transfect C6 cells, Hippocampal neurons, and Cortical neurons. DOTAP stands for 1,2-dioleoyl-3-trimethylammonium-propane and DOPE stands for L-α-dioleoyl-phosphatidylethanolamine.(160)

4.3.6 Liposomes

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Liposomes are the most commonly studied and used nanocarriers.(161) Liposomes are vesicles with an artificial phospholipid bilayer. Many studies have demonstrated successful drug delivery to the brain via liposomes, namely cisplatin for brain tumors, phenytoin for epilepsy, and citicoline for cerebral ischemia.(162-164)

Normally, BBB prevents the passage of hydrophilic and drugs of high molecular weight such as calcitonin. In a previous study, calcitonin was encapsulated in liposomes and its availability in the CNS was studied *in vivo*.(60) The results indicated that calcitonin encapsulated in sulfatide liposomes could cross the BBB and were detectable in the CNS. The areas where biodistribution was observed included the hypothalamus, brain stem, spinal cord, and striatum.(60) In some instances, cholesterol, which is a part of cell membranes, is included in the liposomal constitution, which reduces the permeability of the liposome through BBB and increases the phospholipid bilayers stability .(150, 165, 166)

Cationic liposomes are other types of liposomes frequently studied and used. Genetic drugs can be entrapped in cationic liposomes, thus enabling the protection of the genetic drugs from the extracellular environment and their delivery to the target tissues and cells. The positively charged liposomes and the negatively charged genetic drugs exhibit instantaneous electrostatic interactions. Due to these reactions, cationic liposomes facilitate the transfection of nucleic acids and enable the condensation of nucleic acids efficiently. Unlike the liposomal structures, the cationic liposomes are actually hexagonal structures known as lipoplexes because of the electrostatic interactions.(167) Cationic liposomes that are available for the purpose of gene transfer include [(2,3-dioleyloxy) propyl] -N,N,N-trimethyl-ammonium chloride (DOTMA) and 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP). Their transfection efficacy can be improved by supplementing them with dioleoylphosphatidylethanolamine (DOPE). Addition of cholesterol was another way to improve the transfection efficacy and the stability of liposomes when they were around the serum (Figure 7B).(160)

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4.3.7 Micelles

When dispersed in a liquid phase, 50–100 amphiphilic molecules aggregate together to form a micelle.(168) These amphiphilic molecules contain a head with hydrophilic properties and a tail with hydrophobic properties. When a molecule is designed in this way, it enables hydrophobic drugs to be stored at the center or core of the micelles. Generally, the size of micelles is in the order of 5 to 20 nm in diameter.(92) The ability of micelles to solubilize drugs in their cores and their small sizes make them good carriers for brain drug delivery. Pluronic P85 has been previously shown to affect the permeability of micelles through the BBB using the bovine brain micro vessel endothelial cell monolayer model. Pluronic micelles significantly enhanced the transport of drugs across the BBB. The study showed that the permeability of the drug was increased by a 19-fold.(169, 170)

4.3.8 Improving nanocarrier delivery using targeting strategies

The central hurdle for delivery of any of the aforementioned nanocarrier technologies into the brain is crossing the BBB.(103) Recent reviews have investigated ways to design nanocarriers to cross the BBB more efficiently by using targeting methods.(171-173) Mullis et al. details the importance of targeting strategies for enabling delivery across the BBB, and suggests several ligands used in recent studies that may be utilized for enhancing nanocarrier-mediated brain delivery.(171) These ligands can improve BBB transcytosis of the nanocarrier using one of three methods, including receptor, adsorptive, and cell-mediated transcytosis.(171) This article also emphasizes the importance in enabling nanocarrier targeting downstream of the BBB for optimized therapeutic efficacy.(171) One way to do this could be by designing a nanocarrier that presents ligands temporally.(171) Moreover, while the choice of nanocarrier is important for delivery of neurodegenerative disease therapeutics, so is the choice in targeting ligand for that nanocarrier.

4.4 Conclusions

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Overall, nanotechnology can be used to overcome diagnostic and therapeutic challenges that are associated with neurodegenerative diseases. Previous studies have demonstrated that nanoparticles can cross the BBB both *in vitro* and *in vivo*.(174, 175) This proves that drug delivery systems using nanomaterials can enable and improve brain drug delivery and neurotherapeutic interventions.(20, 176)

5. Nanocarriers in the treatment of neurodegenerative diseases

5.1 Nanocarriers in Alzheimer's disease

The main reason of neurodegeneration in Alzheimer's disease is the accumulation of plaques or amyloid beta protein in the temporal and parietal lobes, which causes changes in cognition, memory loss, hallucination, depression, aggression, agitation, and anger.(177) The majority of the drugs currently available are acetylcholinesterase inhibitors, which delay the breakdown of acetylcholine in the initial stages of the disease.(178) Like the therapies for other neurodegenerative disorders, the biggest obstacle in the treatment of Alzheimer's disease is the inability of molecules to cross the BBB. Nanomaterials can either be used to encapsulate drugs and biologically active agents to combat the disease by targeted delivery, or to reduce the toxicity of plaques by preventing their accumulation.

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is a derivative of quinolone, which is able to solubilize the plaques that accumulate in the neocortex in the extracellular synaptic spaces at the onset of Alzheimer's disease in humans. Clioquinol can also solubilize plaques in transgenic mice models of Alzheimer's disease.(179, 180) Nanomaterials can be used as a carrier to transport clioquinol across the BBB to treat Alzheimer's disease. For example, n-butyl-cyanoacrylate nanoparticles can be used to encapsulate clioquinol for delivery through the BBB.(180) Donepezil is a cholinesterase inhibitor used therapeutically in Alzheimer's disease, which is normally unable to cross the BBB. Bhavna et al.[110] applied PLGA nanoparticles about 83.24 nm to 96.10 nm in size as nanocarriers for donepezil delivery to the brain. Their results demonstrated successful uptake of the nanoparticles in the brain, and the

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pharmacokinetics revealed a burst release at the beginning, which was followed by a slow release in the brain.(181) It has been previously reported that excessive oxidative stress in the brain is involved in neuronal damage and death in patients with Alzheimer's disease. Fullerenols, which are well studied antioxidants (Figure 8A), can be potentially used to prevent the formation of amyloid plaques in Alzheimer's disease.(182, 183)

Early diagnosis of Alzheimer's disease is critical to prevent excessive neuronal damage and unnecessary symptoms by starting the treatment at an early stage. Nanotechnology can be used as a tool to help in the early diagnosis of the disease.(184) There are mainly two ways by which Alzheimer's disease can be diagnosed early. The first method utilizes nanoparticles that are marked with fluorescent probes and the second method utilizes magnetic nanoparticles that can be detected by magnetic resonance imaging. Iron oxide nanoparticles is an example of nanoparticles that are used in magnetic resonance imaging as contrast agents. Monocrystalline iron oxide nanoparticles have been successfully applied to target and envision plaques formed as a result of Alzheimer's disease.(185) The advantages of utilizing iron oxide nanoparticles are large surface area and low toxicity. The FDA has approved the use of these nanoparticles for magnetic resonance imaging of the liver.(184, 186) Furthermore, gold nanoparticles are a good choice for the detection of beta-amyloid plaques and monitoring their alteration.(187) Future *in vitro* and *in vivo* studies are still warranted, especially regarding toxicity, to evaluate their safe use in the diagnosis of Alzheimer's disease.(184) As a hydrophilic fluorescent marker, Thioflavin-T can be used to detect beta-amyloid plaques. However, the problem with this marker is its limited passage across the BBB. In contrast, encapsulating Thioflavin-T in butyl-cyanoacrylate nanoparticles significantly improves their effective transport across the BBB. The accumulation of nanoparticles in the cytoplasm of granule cells and the drug release are illustrated in Figure 8B, thus advancing this method as a promising treatment option in Alzheimer's disease.(188)

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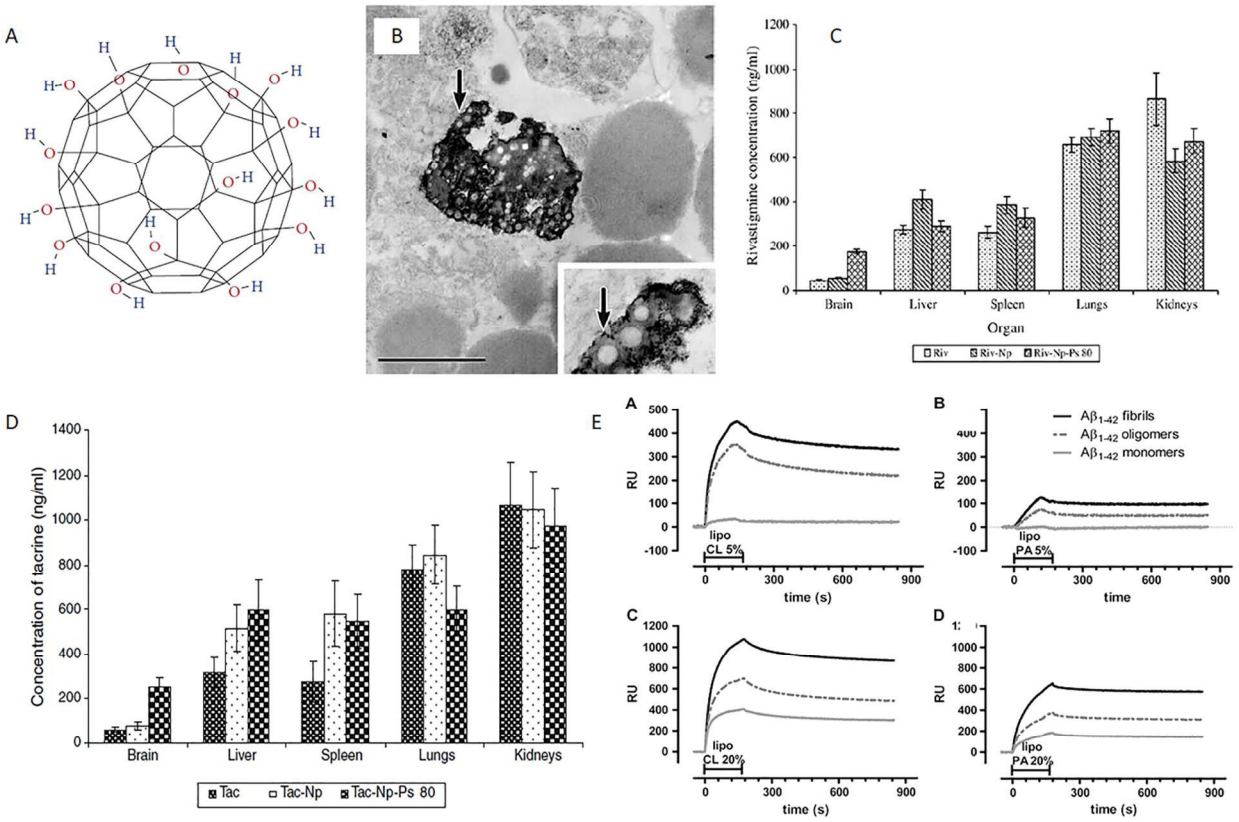

Figure 8 (A) Fullerenol structure.(182) (B) Accumulation of core shell latex particles loaded with Thioflavin-T in the cytoplasm of granule cell. The surrounding material represents the Thioflavin-T released from particles. Scale bar represents 1 µm.(188) (C) Rivastigmine concentration in various organs after intravenous injection to rat models. Riv represents administration on free Rivastigmine. Riv-NP represents poly(n-butylcyanoacrylate) nanoparticle encapsulating Rivastigmine. Riv-NP-PS 80 represents nanoparticles encapsulating Rivastigmine coating with 1% polysorbate 80.(189) (D) Tacrine concentration in various organs after intravenous injection to rat models. Tac represents the administration of free Tacrine. Tac-NP represents poly(n-butylcyanoacrylate) nanoparticle encapsulating Tacrine. Tac-NP-PS 80 represents nanoparticles encapsulating Tacrine coating with 1% polysorbate 80.(190) (E) Resonance units of liposomes over time that represent their preferential binding to β-amyloid monomers, oligomers, or fibrils. All liposomes are constituted of sphingomyelin from bovine brain (Sm) and cholesterol (Chol) (Sm:Chol 1:1). Upper figures have dimyristoylphosphatidic acid (PA) as the third component to combine with Sm and Chol. Lower figures have cardiolipin (CL) as the third component to combine with Sm and Chol. Left figures have 5 molar % and right figures have 20 molar % of the third component.(191)

Another treatment method for Alzheimer's disease is improving the cholinergic neurotransmission. Acetylcholinesterase is an enzyme accountable for the breakdown of acetylcholine; thus, acetylcholinesterase inhibitors can be utilized to inhibit the acetylcholine breakdown, which in turn increases the action levels of acetylcholine. Rivastigmine is a non-competitive and reversible acetylcholinesterase inhibitor that was approved by the FDA for the treatment of Alzheimer's disease in

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2000.(184) Similarly to other agents, nanocarriers can be applied for the rivastigmine transportation through the BBB into the CNS. In a previous study, rivastigmine was encapsulated in poly n-butylcyanoacrylate nanoparticles with coating of polysorbate. Subsequently to intravenous injection, the amount of rivastigmine increased by 3.8 folds in the rat brain (Figure 8C). In another study using tacrine, which is another acetylcholinesterase inhibitor, drug uptake was increased by 4 times in the mouse brain (Figure 8D).(189, 190)

Oxidative damage promoted by metals such as iron, zinc, copper, and aluminum is a cause of Alzheimer's disease. Since these metals create an environment that supports oxidation, the use of chelators to reduce the metals in the brain may be an option for the disease treatment. Studies have shown that nanoparticles attached to chelators could cross the BBB.(178) D-Penicillamine is a copper chelator approved by the FDA with the ability to treat diseases such as Wilson's disease and rheumatoid arthritis.(35) However, the high hydrophilicity of D-Penicillamine prevents its entry through the BBB.(192) Therefore, 1,2 Dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-(4-[p-maleimidophenyl]-butyramide) (sodium salt) (MPB-PE) containing nanoparticles and 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-(3-[2-pyridyldithio]-Propionate) (sodium salt) (PDP-PE) containing nanoparticles were coupled covalently by disulfide bonds to D-penicillamine. Reducing agent dithiothreitol promoted the D-penicillamine release from the nanoparticles, thus demonstrating the successful transport of D-penicillamine across the BBB via nanoparticles. Therefore, D-penicillamine can be used to reduce the amount of metal ions that are known to promote the beta-amyloid deposition in patients with Alzheimer's disease. This nanocarrier system has been reported not to affect the integrity of the BBB.(35, 192)

The ferulic acid is a both an antioxidative and anti-inflammatory in nature. Studies on ferulic acid loaded in SLN have indicated that it can prevent cell death by sparing neurons of oxidative stress.(184, 193, 194) Gobi et al. used SLN and liposomes loaded with phosphatidic acid cardiolipins for the

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treatment of Alzheimer's disease by targeting the beta amyloid plaques.(191) The average size of the nanoparticles used was between 76 nm and 145 nm. Surface plasmon resonance studies were conducted using these nanoparticles and indicated a high affinity towards the beta amyloid fibrils (Figure 8E).(184, 191) Dendrimers are nanosized materials that display a repeated pattern of branching. Chafekar et al. conducted studies using functionalized dendrimers to evaluate their effect on beta amyloid plaques. Their results indicated that the nanoparticles did prevent the accumulation of the plaques, but rather promoted the disintegration of aggregated amyloid plaques.(184, 195)

5.2 Nanomaterials in Parkinson's disease

Parkinson's disease manifests itself after a series of events at the molecular and cellular level, which lead to biochemical and neurological disturbances.(196) Nanomaterials can be used as a tool to advance the treatment of Parkinson's disease via precise control of biological systems. For example, nanotechnology may greatly advance neuroprotection in Parkinson's disease.(4, 197, 198)

Polymeric nanoparticles are studied extensively to promote the drug delivery to the brain to treat Parkinson's disease. The first polymeric nanoparticles crossing the BBB were the poly(butylcyanoacrylate) (PBCA) nanoparticles. Indeed, PBCA nanoparticles coating with polysorbate 80 could cross the BBB and deliver drugs to the brain.(199) Polysorbate 80 coating supports the transport of PBCA into the brain through interacting with the BBB in a manner similar to that of low density lipoproteins.(109) Other polymers used so far included the poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and PLGA, all of which were capable of crossing the BBB to treat Parkinson's disease.(109, 200) Chitosan is a naturally occurring polymer with the ability to form nanoparticles to treat Parkinson's disease. Researchers have shown that chitosan nanoparticles can be useful in delivering peptides and dopamine to the brain. Figure 9A depicts the dopamine concentration in the rat striatum after a single chitosan nanoparticle injection. As stated before, the symptoms of Parkinson's disease are largely due to

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the reduction in the levels of dopamine. Therefore, chitosan nanoparticles can be potentially used as carriers to transport dopamine to the CNS to treat Parkinson's disease. (109, 201, 202)

In terms of nanocarrier targeting strategies, several studies have examined using targeting ligands to further improve therapeutic efficacy of nanocarriers for Parkinson's Disease treatments.(203, 204) For example, Hernando et al. investigated using transactivator of transcription peptide conjugated to a lipid carrier, and found that the efficacy of the encapsulated therapeutic, glial cell-derived neurotrophic factor, was improved.(203) In another study, Wen et al. conjugated a lectin derivative, Odorranalectin, to PLGA-based nanoparticles to improve delivery across the nose-brain barrier.(204) In both of these studies, overcoming the BBB was achieved by essentially bypassing it using intranasal delivery as the method of administration.

Gene delivery to the CNS with the help of nanocarriers can potentially support the treatment of Parkinson's disease. Gene delivery can be used to alter the capability of the brain to regenerate and improve compensatory mechanisms, and further treat other brain pathological processes.(198, 205) Neurotrophic factors are responsible for the growth and development of brain cells. A majority of the symptoms associated with Parkinson's disease are associated with a reduction in the amount of dopamine production. Neurotrophic factors can boost brain cell survival and increase dopamine level. Thus, delivering genes that code for neurotrophic factors with the help of nanocarriers can potentially prevent brain cell death and mitigate the disease symptoms.(206, 207)

Other nanomaterials applied in Parkinson's disease include the use of fullerenols. Fullerenols are obtained from buckminsterfullerene (C60), which is known to prevent apoptosis, glutamate receptor action, and neuronal oxidation (Figure 9B).(208) Carbon nanotubes can be also used as wireless biosensors in the treatment of Parkinson's disease. Carbon nanotubes arranged to form a carbon nanochip are able to keep track of dopamine level changes and to maintain it at a controlled level.

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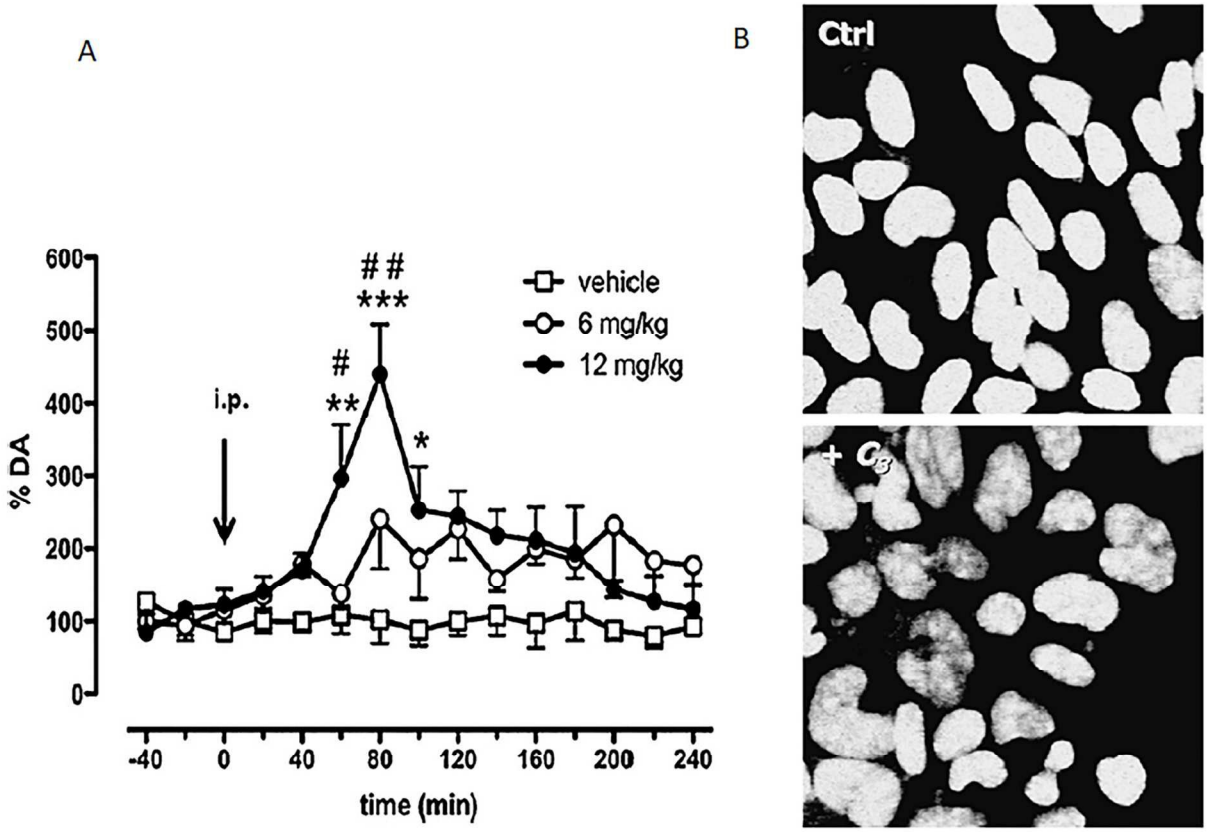

Figure 9 (A) The percent of dopamine in rat striatum in a 4-h time period. Single dosage (6–12 mg/kg) was injected. DA stands for dopamine. Vehicle = chitosan nano particles (CSNP). CSNP stands for chitosan nanoparticles. *p < 0.05, **p < 0.01, ***p < 0.001 *versus* respective vehicle; #p < 0.05, ##p < 0.01 *versus* respective DA/CSNPs (5) (6 mg/kg). Arrow shows the administration time.(202) (B) Confocal microscopy of cortical astrocytes treated with vehicle (H_2O) (upper) and C_3 fullerene (the tris malonic acid C60 adducts) (lower). Superoxide-sensitive dihydroethidium (DHE) was used as the fluorescent compound and decreasing fluorescent in the sample containing C_3 showed that C_3 resulted in lower mitochondrial superoxide anion production.(208)

5.3 Nanomaterials in Huntington's disease

Huntington's disease is a genetic disorder featuring cognitive symptoms, motor symptoms, chorea, dementia, and psychosis. Almost 40% of the patients diagnosed with the disease suffer from depression, and the disease is often mistaken with schizophrenia because of their shared symptoms.(209) Similarly to Alzheimer's disease and Parkinson's disease, nanocarriers can be used as a tool to deliver drugs and therapeutics across the BBB to treat Huntington's disease.

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Free radicals in the brain are formed as a result of oxidation, and remain in the brain mainly due to poor anti-oxidant activity, thus leading to neuronal damage and death. Poor antioxidant defense in the brain can also cause neuronal death in the case of neurodegenerative diseases, such as Huntington's disease. Hence, antioxidants can be used as therapeutics to prevent oxidative stress in Huntington's disease.(182) Fullerenols, which are derivatives of fullerenes, are hydrophilic and able to clear surrounding free radicals; indeed, fullerenols are commonly referred to as radical sponges due to their ability to remove free radicals.(182) Their anti-oxidant nature and spherical, hollow shape make them ideal carriers for the treatment of Huntington's disease. The anti-oxidant nature of fullerenols has been demonstrated repetitively. Jin et al. reported that fullerenols were effective in blocking glutamate receptors in an antagonistic nature and can therefore be used for neuroprotective applications (Figure 10A).(210)

The application of SLN have been investigated extensively for the treatment of neurodegenerative diseases and delivery of the drug to the CNS. SLN are lipidic nanocarriers, which enables them to move more readily across the BBB into the brain. Nitrendipine is a dihydropyridine calcium channel blocker that reduces the incidences of dementia in Huntington's disease by a margin of 50% in a span of 2 years,(211) thus exerting neuroprotective effects.(212) However, being hydrophilic in nature, nitrendipine cannot cross the BBB effectively. In one study that compared the uptake of nitrendipine when administered normally and when administered using SLN, nitrendipine was encapsulated in SLN made of a mixture of glycerides, namely, tripalmitin, trimyristin, and tristearin. The results indicated an increase in nitrendipine uptake by the brain when SLN were used ,(157) suggesting their potential use in the treatment of Huntington's disease. In another study, modified cyclodextrin was used to encapsulate short-interfering RNA (siRNA) with the aim of decreasing the expression of mutant huntingtin (HTT) gene. This strategy resulted in the reduced expression of HTT mRNA both *in vivo* and *in vitro* as well as a low cytotoxic effect (Figure 10B) (213, 214) Although a detailed description of the positive aspects of the

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use of self-assembled chitosan nanomaterials in drug delivery was provided, there was no mention of any drawbacks using these systems, e.g., scale-up. For a critical review of the field, more effort is needed to present both the beneficial and unfavorable effects from different aspects.

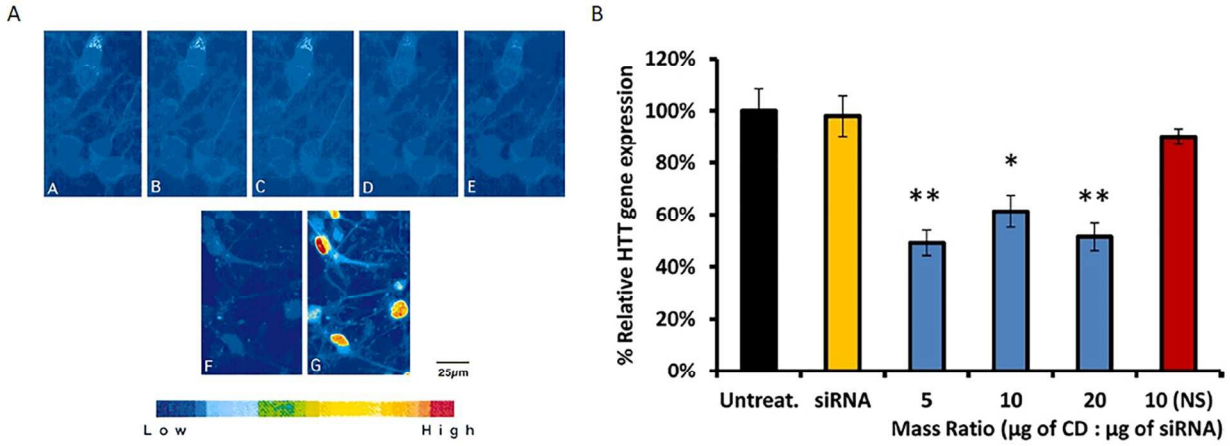

Figure 10 (A) Glutamate (Glu) receptors blocking of fullerenol. Glu induced free intracellular calcium is believed to be the reason for neurotoxicity. Cultures A-E all were treated with 50 μM fullerenol. Sample A contained no Glu, B-E related to the 0.5, 1, 3, and 5 minutes after treatment with Glu, F contained no Glu and no fullerenol and G contained no fullerenol but, 0.25 mM of Glu. Comparison between G and E clearly showed the effect of fullerenol on free calcium decrease.(210) (B) The effect of short-interfering RNA (siRNA)-loaded modified cyclodextrin (CD) on the mutant Huntington (HTT) gene expression in a rat striatal cell line. Knockdown of HTT gene expression was obtained with PCR.(214)

Table 1 summarizes some of the studies conducted using nanoparticles in the treatment or diagnosis of neurodegenerative diseases.

Table 1. Nanoparticles used in neurodegenerative disease

Disease	Types of nanoparticles used for treatment	Size range	Advantages	Surface modification/Coating	References
Alzheimer's Disease	SLN	93.20–99.12 nm(194), 76–145 nm(191)	High affinity of SLN to beta amyloid fibrils		Picone et al(194), Gobi et al.(191)
	Dendrimers	20–80 nm(195)	Regular and highly branched structures, size, and structural resemblance to protein molecules		Chafekar et al.(195)

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	PLGA[1] nanoparticles	83.24–96.10 nm(181)	Biocompatibility and biodegradability	Polysorbate coating	Bhavna et al.(181)
	PBCA[2]	33.6–47.4 nm(189)	Ability to cross the BBB (BBB) efficiently	Polysorbate coating	Wilson et al.(189, 190), Roney et al.(180)
	1,2-(dimethoxymethano) fullerene		Inhibition of amyloid peptide aggregation at the first stages with a large inhibitory constant		Kim et al.(183)
	MION[3]		Early detection of amyloid plaques		Wadghiri et al.(185)
	Co@Pt nanoparticles	15 nm(187)	Improved magnetic properties, high colloidal stability, early detection of Aβ plaque, and probe of protein self-assembly	Au	Choi et al.(187)
	Thioflavin-T-containing core-shell latex particles	90 nm(188)	Localization of nanoparticles intracellularly to prevent synthesis of Aβ plaques and extracellularly to prevent Aβ plaque formation		Hartig et al.(188)
Parkinson's Disease	PLGA		Good biodegradability and ability to control the rate of biodegradability	Polysorbate 80 surface coating	Patel et al.(109, 188)
	Carbon Nanotubes		Light weight, high mechanical strength, and inert chemically		Modi et al.(20)

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	Chitosan	67-147 nm(202)	Biodegradable, biocompatible, low toxicity, and good uptake of hydrophilic drugs and peptides	Polysorbate 80 coating	Trapani et al.(202) Patel et al.(109), Mao et al.(215)
	PBCA	118-179.2 nm(216)	Easy fabrication, ability to cross the BBB efficiently	Non-ionic surfactant - polysorbate 80	Patel et al.(109), Olivier(199), Lin et al.(216)
Huntington's Disease	Fullerenols		Hollow and spherical structure, anti-oxidant properties, and ability to remove free radicals- "radical sponge"		Grebowski et al.(182), Jin et al.(210), Injac et al.(217)
	SLN [NDP-Nitrendipine] [TP-Tripalmitin]	105.8–108.6 nm(157) (NDP-TP-DCP) 106.7–110.5 nm (NDP-TP-SA)	Increased bioavailability, good for controlled and targeted drug delivery, reproducibility, stability, and lower toxicity	Surface charge modifiers- dicetyl phosphate (DCP), stearylamine (SA).	Manjunath et al.(157), Kaur et al.(154)
	B-Cyclodextrin	100–350 nm(214)	Huntingtin (HTT) gene silencing, favorable cell toxicity		Godinho et al.(214)

[1] *Poly(lactic-co-glycolic acid)*
[2] *Poly(n-butylcyanoacrylate)*
[3] *Monocrystalline iron oxide nanoparticles*

6. Conclusions and perspectives

Based on a large body of literature, it is evident that nanocarriers represent the future of drug delivery to the CNS. The BBB is selective to the entry of limited molecules, which helps prevent the intrusion of harmful molecules into the CNS. However, this protective feature of the BBB is also the biggest hurdle in the delivery of drugs for the treatment of neurodegenerative diseases. Nanocarriers can cross the BBB and can thus be used as a tool for brain drug delivery. Inability of the drugs to cross

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the BBB can be enhanced by their encapsulation inside the nanocarriers to facilitate their entry into the brain. This procedure is non-invasive and drugs trapped in nanocarriers can be administered intravenously. The main advantage of engineered nanoscale drug delivery systems is that the drug or the active component is not involved in the obstacles of transporting the drugs to the target area. Thus, nanocarriers can be engineered in the desirable way without involving or changing the drug.

The main challenges for nanoparticles used for this purpose, especially when targeting the brain, are biodegradability, biocompatibility, and non-toxicity. Another limitation that needs to be overcome is the low encapsulation efficiency of some drugs. Non-biodegradable nanoparticles can accumulate in the brain and turn into toxic substances, thus resulting in complications. Due to the limited data available from *in vivo* and clinical studies regarding the use of nanoparticles for drug delivery into the CNS, potential toxic side effects are still unknown. Therefore, further research is still warranted to validate the potential therapeutic use of nanocarriers to treat neurodegenerative diseases.

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Figure captions

Figure 1. Overall scope of neurodegenerative diseases

Figure 2. Causes, symptoms, and general treatments of neurodegenerative diseases

Figure 3. Capillary structures of the BBB

Figure 4. Transport pathways of endothelial cells in the BBB

Figure 5. Available forms of nanoparticles that are used in the treatment of neurodegenerative diseases

Figure 6. (A) polymer-lipid nanoparticle (PLN) formation. D^+ represents the water-soluble cationic drug molecule and curved line shows the anionic polymer chain. The charges of the two molecule are neutralized and results in the PLN formation.(152) (B) Transmission electron microscopy (TEM) of blank Solid lipid nanoparticles (SLN) and Actarit-loaded SLN (right).(153) (C) Scanning electron microscopy (SEM) of dry powder inhalation (DPI) system of SLN loaded with insulin.(155) (D) Cytotoxicity comparison of the Dynasan-SLN (□), Compritol-SLN (●), polyhexylcyanoacrylate (+), and polymethylcyanoacrylate (Δ) nanoparticles in contact with human promyelotic HL60 cell lines. Cells showed higher viability exposed to SLN nanoparticles compared to the reference drug carriers.(156)

Figure 7. (A) Nanoemulsion (left) and Macroemulsion (right).(158) (B) The effect of liposome composition on cell transfection. Cholesterol in a cationic liposome formulation, such as DOTAP, acts as a helper lipid to transfect C6 cells, Hippocampal neurons, and Cortical neurons. DOTAP stands for 1,2-dioleoyl-3-trimethylammonium-propane and DOPE stands for L-α-dioleoyl-phosphatidylethanolamine. (160)

Figure 8. (A) Fullerenol structure.(182) (B) Accumulation of core shell latex particles loaded with Thioflavin-T in the cytoplasm of granule cell. The surrounding material represents the Thioflavin-T released from particles. Scale bar represents 1 μm.(188) (C) Rivastigmine concentration in various organs after intravenous injection to rat models. Riv represents administration on free Rivastigmine. Riv-NP represents Rivastigmine loaded poly(n-butylcyanoacrylate) nanoparticle. Riv-NP-PS 80 represents nanoparticles encapsulating Rivastigmine coating with 1% polysorbate 80.(189) (D) Tacrine concentration in various organs after intravenous injection to rat models. Tac represents the administration of free Tacrine. Tac-NP represents Tacrine loaded poly(n-butylcyanoacrylate) nanoparticle. Tac-NP-PS 80 represents nanoparticles encapsulating Tacrine coating with 1% polysorbate 80.(190) (E) Resonance units of liposomes over time that represent their preferential binding to β-amyloid monomers, oligomers, or fibrils. All liposomes are constituted of sphingomyelin from bovine brain (Sm) and cholesterol (Chol) (Sm:Chol 1:1). Upper figures have dimyristoylphosphatidic acid (PA) as the third component to combine with Sm and Chol. Lower figures have cardiolipin (CL) as the third component to combine with Sm and Chol. Left figures have 5 molar % and right figures have 20 molar % of the third component.(191)

Figure 9. (A) The percent of dopamine in rat striatum in a 4-h time period. Single dosage (6–12 mg/kg) was injected. DA stands for dopamine. Vehicle = chitosan nano particles (CSNP). CSNP stands for

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chitosan nanoparticles. *p < 0.05, **p < 0.01, ***p < 0.001 *versus* respective vehicle; #p < 0.05, ##p < 0.01 *versus* respective DA/CSNPs (5) (6 mg/kg). Arrow shows the administration time.(202) (B) Confocal microscopy of cortical astrocytes treated with vehicle (H_2O) (upper) and C_3 fullerene (the tris malonic acid C60 adducts) (lower). Superoxide-sensitive dihydroethidium (DHE) was used as the fluorescent compound and decreasing fluorescent in the sample containing C_3 showed that C_3 resulted in lower mitochondrial superoxide anion production.(208)

Figure 10. (A) Glutamate (Glu) receptors blocking of fullerenol. Glu induced free intracellular calcium is believed to be the reason for neurotoxicity. Cultures A-E all were treated with 50 μM fullerenol. Sample A contained no Glu, B-E related to the 0.5, 1, 3, and 5 minutes after treatment with Glu, F contained no Glu and no fullerenol and G contained no fullerenol but, 0.25 mM of Glu. Comparison between G and E clearly showed the effect of fullerenol on free calcium decrease.(210) (B) The effect of short-interfering RNA (siRNA)-loaded modified cyclodextrin (CD) on the mutant Huntington (HTT) gene expression in a rat striatal cell line. Knockdown of HTT gene expression was obtained with PCR.(214)

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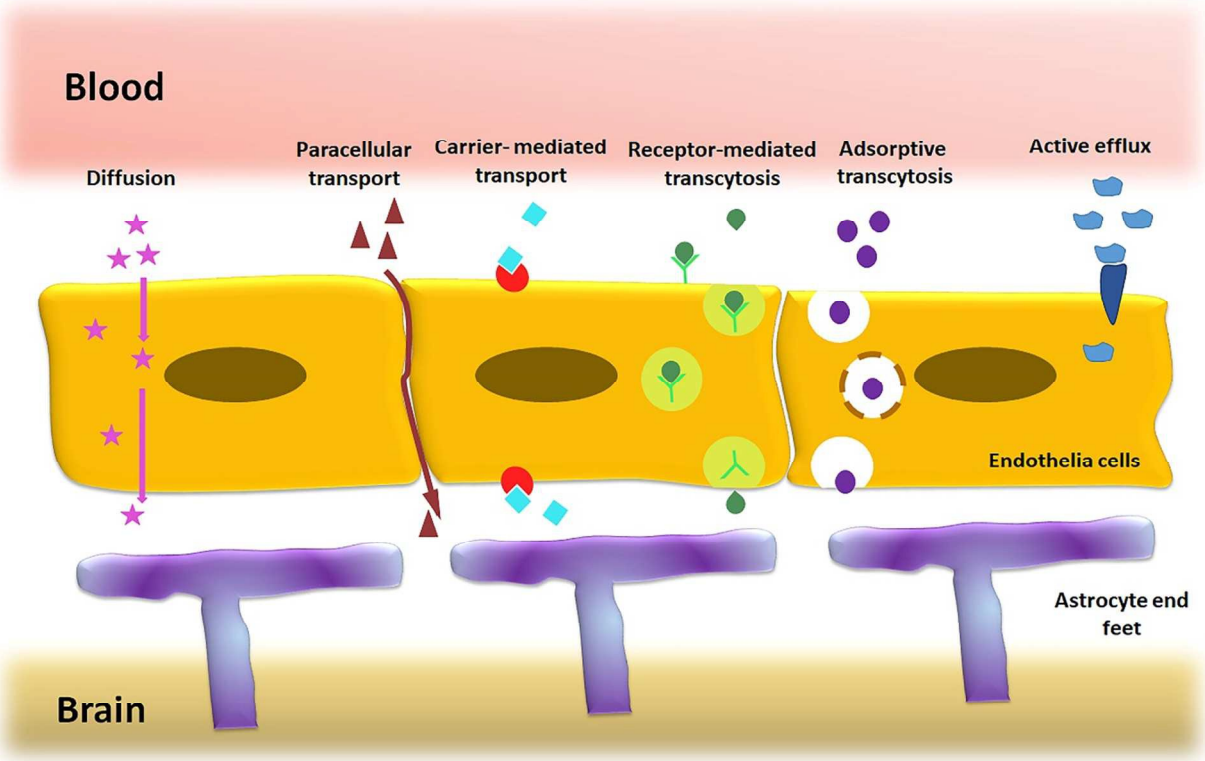

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This review highlights the recent advancements in the preparations and applications of nanocarriers for the treatment of neurodegenerative disorders through the blood-brain barrier.