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Review Article

Nanotechnology-Driven Approaches in Overcoming Drug Delivery Challenges for Neurodegenerative Diseases

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ABSTRACT

The management of Neurodegenerative Diseases (NDs) is a substantial concern for healthcare systems at present. Alzheimer's disease, frontotemporal dementia, Parkinson's disease, prion disease, Huntington's disease and Amyotrophic lateral sclerosis are among these conditions. Pathogenic characteristics shared by these conditions include increased oxidative stress, misfolded proteins, dysfunctional mitochondria, excitotoxicity and neuro inflammation; these ultimately result in the deterioration of the structure and function of the nervous system. Despite extensive testing, there is currently no specific medication available to halt or cure the progression of these diseases. Therapy failure in neurodegenerative illnesses is often linked to the limitations posed by P-glycoproteins, the blood-brain barrier and the blood-cerebrospinal fluid barrier. Nevertheless, recent progress in nanotechnology presents an encouraging avenue for overcoming these constraints. By leveraging nanotechnology and developing nanomaterials that facilitate the delivery of active drug candidates, there is potential to overcome these challenges. Various approaches are being explored, including drug distribution through local delivery, physicochemical disruption of the blood-brain barrier, cell-penetrating peptides, receptor-mediated transcytosis and magnetic disruption. These methods aim to surmount the obstacles associated with drug delivery. This review succinctly covers the mechanism of nanoparticles, different types of nanoparticles used in treating NDs and potential future applications of nanotechnology in clinical neuroscience. The ultimate goal is to develop innovative therapeutic strategies for effectively managing and treating neurodegenerative diseases.

Keywords: Alzheimer's disease, Drug delivery, Frontotemporal dementia, Neurodegenerative diseases, Parkinson's disease, Nanotechnology.

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INTRODUCTION

The ageing population suffers an increase in age-related illnesses such as cancer, heart disease neurological problems, especially for individuals 65 years of age and older. According to the 2019 Global Burden of Disease Study, neurological disorders account for 8% of the global health burden.[1] These illnesses are incurable and may have a significant negative influence on memory, motor skills, language cognition. A few examples of these diseases include Alzheimer's Disease (AD), Huntington's Disease (HD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), glioma and prion disease. The global well-being of patients is seriously threatened by their rising prevalence.[2-4]

Despite differences in clinical manifestations, these disorders share commonalities in their pathophysiology, including

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neuroinflammation, neural cell loss, oxidative stress, mitochondrial dysfunction and protein aggregation.[5-7] Although there have been notable strides in understanding and treating these diseases, the outcomes have not met expectations. Current therapies focus on managing symptoms rather than affecting a cure.[8]

One of the most important roles of the Blood-Brain Barrier (BBB) is to keep the environment stable for neuronal activities.[9] However; the BBB's constraints make it difficult to provide therapies for illnesses of the Central Nervous System (CNS). Two main strategies for crossing the BBB exist invasive and non-invasive approaches.[10] Nanoparticles have garnered significant attention due to their advantages, such as high drug-loading capacity, minimal systemic toxicity, chemical stability, modifiable therapeutic properties and enhanced drug permeability.[11-17] However, the efficacy of nanoparticles in crossing the BBB is heavily influenced by factors such as their nature, size, surface chemistry and polarity.[18]

This study aims to provide a broad overview of neurodegenerative illnesses, present challenges, and possible remedies. Furthermore, it will investigate the present state of nanomaterials and their use in administering medications for conditions affecting the nervous system.

Neurodegenerative Diseases

A group of illnesses known as Neurodegenerative Diseases (NDs) are characterised by a steady decline in the structure and functionality of the nervous system. These illnesses, which primarily affect brain and sometimes spinal cord neurons, may result in a variety of behavioural, motor and cognitive issues.[19] Distinguished NDs consist of: Alzheimer's disease: A gradual loss of cognitive function, memory and reasoning ability are the hallmarks of this common neurological illness. It has been connected to the build-up of aberrant protein deposits in the brain, including beta-amyloid plaques and tau tangles.[20]

Parkinson's disease

This condition is characterized by muscle rigidity, tremors and sluggish movement (bradykinesia), all of which primarily affect movement. It is caused by the degeneration of neurons in the substantia nigra of the brain that produce dopamine.[21]

Huntington's disease

A hereditary condition causing uncontrollable movements, emotional fluctuations and cognitive impairment, it is associated with a mutation in the HTT gene.[22]

Amyotrophic Lateral Sclerosis (ALS)

Respiratory failure, paralysis and weakening of the muscles are the results of this progressive motor neuron disease, which causes the death of motor neurons in the brain and spinal cord.[23]

Multiple Sclerosis (MS)

While not classified as a neurodegenerative disease, MS involves the gradual deterioration of the myelin sheath around the central nervous system, causing symptoms like fatigue, poor coordination and muscle weakness.[24]

Frontotemporal Dementia (FTD)

This term exhibits a set of disorders that predominantly impact the frontal and temporal regions of the brain, resulting in alterations in behaviour, character and language skills.[25]

Prion Disorders

These diseases, including Creutzfeldt-Jakob disease, originate from misfolded proteins known as prions. They can trigger the misfolding of other normal proteins, leading to progressive and fatal neurological degeneration.[26]

Spinocerebellar ataxias (SCAs)

Hereditary disorders affecting the spinal cord and cerebellum, SCAs result in issues related to balance and coordination.[27]

Progressive supranuclear palsy (PSP)

An uncommon neurological condition impairing cognition, balance and movement, it is distinguished by the abnormal accumulation of tau proteins in the brain.[28]

The precise aetiology of most neurodegenerative disorders remains unknown and effective treatments are often lacking. However, ongoing research aims to deepen our understanding of these diseases, develop interventions to slow their progression and enhancement of the affected individuals' quality of life. Early diagnosis and symptom management can assist individuals and their families in coping with these challenging conditions.

Contemporary Methods for Treating Neurodegenerative Disorders

The management of neurodegenerative disorders is usually customized to suit the specific requirements of individual patients. Currently, multiple established treatment methods focus on understanding the cause of the disease or aim to alleviate its symptoms. This study examines the primary NDs that are presently undergoing treatment through diverse therapeutic approaches (Table 1).

Table 1: Alternative methods for treating neurodegenerative conditions at present.

Neurological Disorder	Drug Class	Mechanism	Drugs
Alzheimer disease	Amyloid-directed antibody	Targeting and eliminating amyloid-beta plaques.	Aducanumab
	Glutamate regulators	N-methyl-D-aspartate (NMDA) receptor antagonism to enhance glutamatergic transmission signal-to-noise ratio.	Memantine
	Cholinesterase Inhibitors	Prevent the knockdown of acetylcholine.	Donepezil, rivastigmine, galantamine.
Parkinson disease	Dopamine agonist	Produces dopamine-like effects.	Apomorphine hydrochloride, pergolide, pramipexole dihydrochloride, ropinirole hydrochloride, rotigotine.
	Dopamine supplements	Replenish the decreased levels of dopamine.	Levodopa
	Decarboxylase inhibitors	Prevent levodopa's peripheral breakdown.	Carbidopa
Amyotrophic Lateral Sclerosis	Free-radical scavenger	Scavenges free radicals.	Edaravone
	Glutamate-receptor antagonist	Inhibits glutamate receptors	Riluzole

Therapeutic Approaches for Alzheimer's Disease (AD)

The primary objective of therapeutic interventions in managing AD is to target multiple pathways implicated in the progression of the disease. Currently, the US FDA has approved three classes of medications for treating AD, which are outlined below.

Targeting Amyloid-Beta (Aβ) Plaques with Antibodies

In June 2021, Aducanumab (Aduhelm) received approval as the first disease-modifying drug for individuals with AD.[29] Administered Intravenously (IV) every four weeks over approximately an hour, this IgG1 monoclonal antibody is designed to focus on the extracellular Aβ plaques within the brain, binding to and facilitating their removal.[29,30] While clinical trials on aducanumab, though conditionally licensed, have indicated a reduction in Aβ plaque burden, there is no clear correlation with increased patient's cognitive performance. Further clinical data is required to provide definitive evidence of the drug's potential benefits for cognitive functions. Despite this, AD patients and advocacy groups have expressed enthusiasm over aducanumab's approval. In addition to being the inaugural treatment aimed at tackling the changes in the disease's underlying mechanisms, they are optimistic that it will set the stage for the development of similar treatments in the upcoming period.

Numerous bioactive compounds, such as therapeutic antibodies and secretase inhibitors, have been utilized in various clinical trials, but most of these trials have concluded thus far. AAB-003, MEDI1814, RO7126209, SAR228810 and other Aβ-targeting antibodies have completed phase I clinical trials. Aducanumab, despite completing phase III clinical trials, remains specific to Aβ aggregation. Similarly, gosuranemab is in phase 2 of clinical trials, while tau or TREM2-specific antibodies, such as BIIB076, bepranemab and JNJ-63733657, have concluded phase I clinical trials.[31] Consequently, more antibody-based targeted medications may soon receive FDA approval for AD treatment.

Cholinesterase Inhibitors

Cholinesterase Inhibitors (CI) are the pharmaceutical treatment of choice for AD currently. In therapeutic contexts, galantamine, donepezil and rivastigmine are the three most frequently used CIs. In AD, cholinergic neurons are lost along with acetylcholine levels in the brain's cortical areas diminish. Several studies have demonstrated that elevated acetylcholine levels in individuals with dementia mitigate their cognitive decline. Enhanced cholinergic activity benefits the patient by limiting acetylcholine breakdown through cholinesterase inhibitors.[32]

The FDA initially approved tacrine as a choline esterase inhibitor in 1993, but it was later discontinued due to hepatotoxicity. Donepezil, taken orally as 5 or 10 mg pills per day, is approved for AD with mild to moderate severity. Recently, higher dosages of donepezil (23 mg/day) and/or memantine have been authorised for individuals with moderate-to-severe disorders. Rivastigmine is utilised as a further AChE inhibitor for mild-to-moderate AD. Unlike other cholinesterase inhibitors, rivastigmine acts as a transdermal patch that inhibits the enzymes Butyrylcholoineserase (BChE) and Acetycholinesterase (AchE). For mild-to-moderate AD, galantamine, the next in line of cholinesterase inhibitors, is licenced at a dosage range of 16-24 mg/day. It also allosterically alters nicotinic cholinergic receptors in addition to blocking cholinesterase activity.[33]

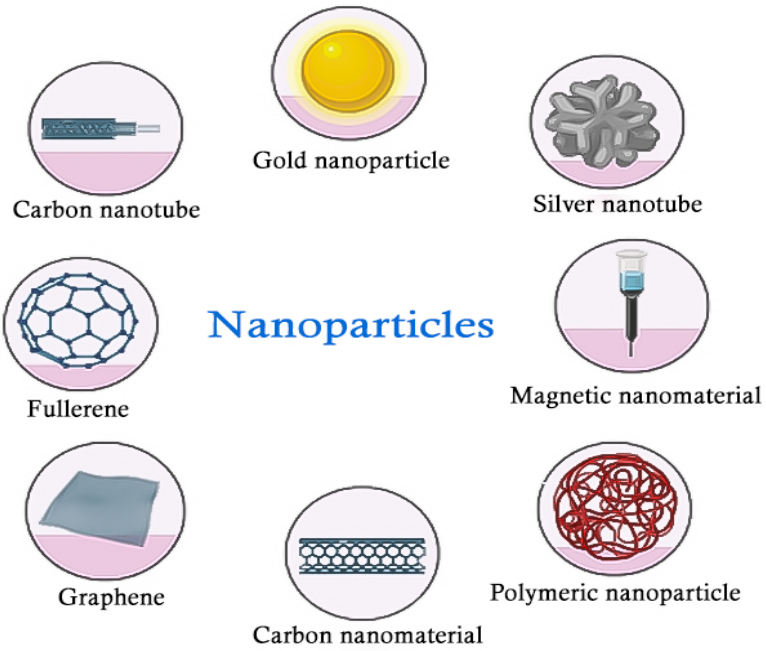

Figure 1: Schematic representation of nanomaterial used in the treatment of NDs.

Despite the development of numerous medications, cholinesterase inhibitors remain the only available treatment for AD. Aducanumab, a recently licensed drug, is contentious in its efficacy and comes with a prohibitive cost. Cholinesterase inhibitors, however, have limited efficacy, classified as symptomatic therapy options that only marginally improve patient's cognitive abilities.[34] Furthermore, it has yet unknown whether the medications that are already on the market can successfully cross the BBB at levels high enough to have the desired pharmacological efficacies.

Glutamate Regulators

Glutamate serves as the primary neurotransmitter that stimulates brain activity. Excessive stimulation of postsynaptic neurons, like NMDA receptors, by glutamate can lead to harm and the degeneration of neurons. Nevertheless, completely blocking NMDA receptors can result in serious side effects. As a result, memantine, an uncompetitive antagonist of NMDA receptors, was created to address this issue. It shields patients from the inhibitory effects of overactivation while providing pathological benefits through NMDA receptor activation.[35]

Memantine was authorised for usage in 2003 at a dosage of 5-20 mg per day for those with moderate-to-severe AD. Compared to a placebo, memantine monotherapy enhanced cognition in AD patients. Clinical trials with AChE inhibitors demonstrated improved efficacy compared to monotherapy after a year.[36,37] However, this class of medications, primarily used for symptom management, also falls short in addressing the pathology of AD.

Therapeutic Approaches for Parkinson's Disease (PD)

Despite being the second most prevalent NDs, there is currently no treatment for PD that specifically alters the disease's aetiology. Instead, several solutions focus on providing symptomatic relief for patients, targeting both non-motor-related and motor-related issues independently.

Improving dopamine levels in the brain's substantia nigra region is an essential part of PD treatment. Many strategies have been used to do this. The primary treatment method frequently utilized combines levodopa and carbidopa. Levodopa, a direct precursor to dopamine, aids in the restoration of motor function in cases of low dopamine levels. Carbidopa is combined with levodopa to safeguard it from breaking down in peripheral tissues before it can reach the brain. Furthermore, Catechol-O-Methyl Transferase (COMT) methylation of levodopa is inhibited by entacapone and tolcapone, which stops levodopa from being lost because of methylation.

Parkinson's disease may also be treated with dopaminergic agonists such pramipexole dihydrochloride, apomorphine hydrochloride, pergolide rotigotine and ropinirole hydrochloride. These agents imitate the effects of dopamine. Another category of medications is monoamine oxidase inhibitors, which are the subsequently available option. These inhibitors hinder the degradation of dopamine in the brain by obstructing its oxidative deamination process. Selegiline and rasagiline serve as illustrations of monoamine oxidase inhibitors.[38]

Like all NDs, PD is linked to considerable Non-Motor Symptoms (NMS), which are managed symptomatically and include depression, psychosis, constipation, sleep disturbances, dementia

Figure 2: Desired features of nanomaterials.

and olfactory impairment.[39] Galantamine, donepezil and rivastigmine are administered to treat symptoms associated with dementia. Pimavanserin, clozapine and quetiapine are approved drugs for managing symptoms related to psychosis. Melatonin or clonazepam should be used for sleep-related issues.[40]

Therapeutic Approaches for Amyotrophic Lateral Sclerosis (ALS)

As ALS, a motor neuron disease, advances, patients might encounter behavioural changes, cognitive decline and symptoms resembling frontotemporal dementia. People with ALS usually die three to five years after developing symptoms and they usually have respiratory failure.[41] Riluzole and edaravone are the two accepted therapies for individuals diagnosed with ALS. In 1995, Riluzole, a drug that blocks glutamate receptors, was initially approved for use in the form of a 100 mg oral tablet to be taken daily. Studies have shown that individuals with ALS who take riluzole typically have a lifespan extended by approximately three to four months compared to those receiving a placebo. In 2017, Edaravone, a free-radical scavenger that aids in slowing the progression of the disease, received approval for intravenous infusion at a daily dosage of 60 mg.[42] Apart from these medications, patients receive symptomatic care to enhance their quality of life. At present, there are no effective treatments capable of modifying the course of ALS.

Challenges of Brain-Drug Delivery

Current treatments mostly aim to delay the disease's development rather than treating the underlying causes of NDs. However, these treatments often fall short of effectively targeting the underlying neurodegenerative issues beyond the BBB. The limited ability of ND treatments to deliver sufficient doses to the brain restricts their effectiveness. The challenges in treating NDs stem from the mature nature of the BBB, which hinders the penetration of most medications.

Understanding the Blood-Brain Barrier

The BBB serves as a diffusion barrier, safeguarding the brain by preventing the entry of chemicals from the bloodstream and maintaining normal brain function.[43] This barrier is established by the fusion of various brain cell types, including basal membranes, tight junctions, neurons, astrocytes and brain microvascular endothelial cells, which create a tightly sealed brain capillary within the BBB.[44] The absence of openings in the endothelial cells of brain capillaries hinders the movement of proteins and small molecules.[45,46] Inter-endothelial junctions form a continuous barrier that limits the passage of water-soluble chemicals.[47,48] Furthermore, the endothelial cells' surrounding astrocytes, pericytes and basal lamina obstruct the flow of drug molecules from the circulation into the brain.[49] Efflux transporters in brain capillaries reinforce this barrier by transporting chemicals back into the bloodstream.[50] Adherens junctions, gap junctions and

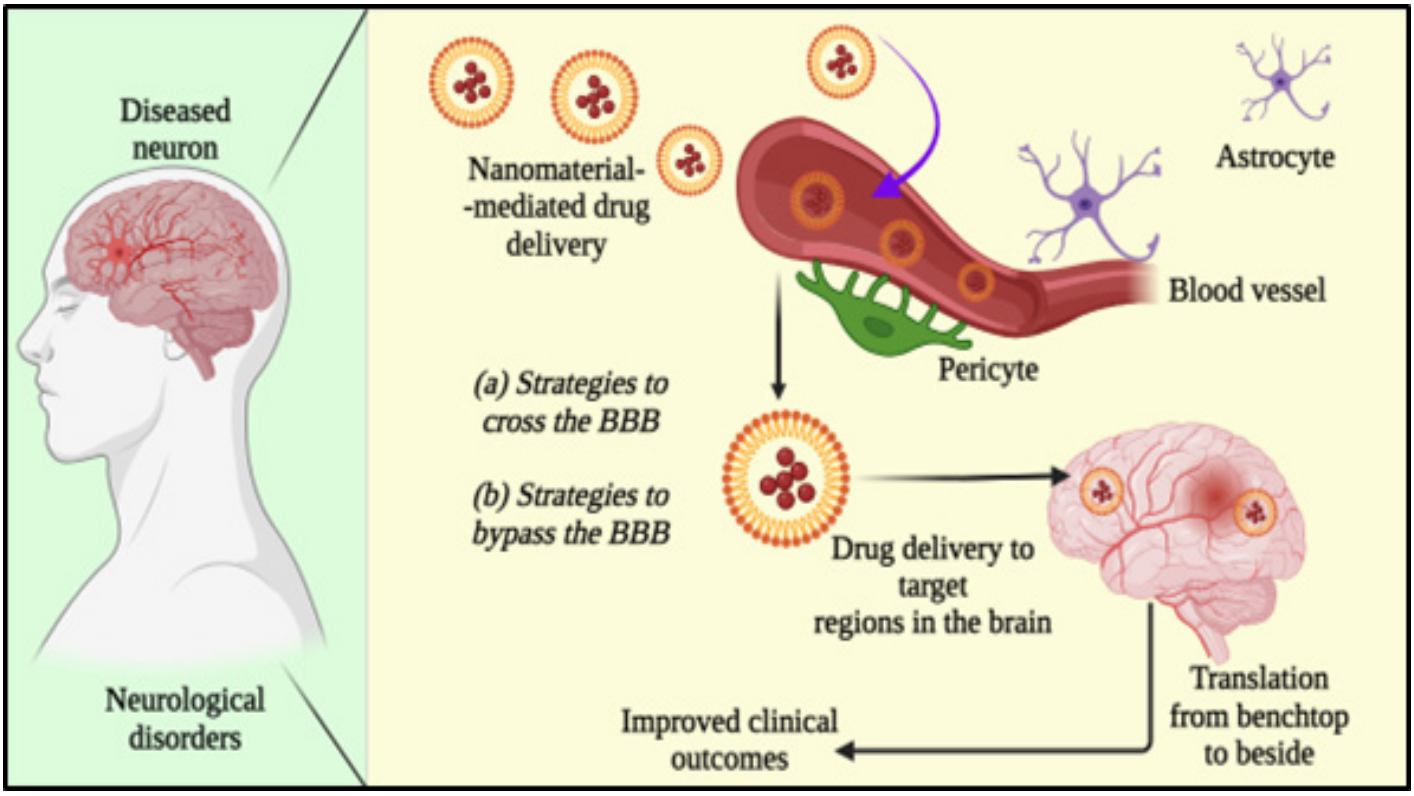

Figure 3: Nanomaterials delivered therapeutic drugs to ND patients' brains to enhance clinical results.

tight junctions together control the permeability function of the BBB.[45,51] Either the transcellular or paracellular route is used by molecules to cross the BBB.[51] Compound transport across the BBB is affected by factors like their physical and chemical properties, which include dimensions, molecular mass, surface reactivity, lipid compatibility and electrical charge.[52,53] The BBB permits the unrestricted passage of certain small molecules via passive diffusion, including carbon dioxide, ethanol and barbiturates.[54,55] Hydrophilic molecules like peptides and proteins are transported through receptor-mediated transport systems, examples like the insulin carrier, Glucose Transporter-1 (GLUT-1) and transferrin receptor.[56,54] The BBB can be compromised by certain pathological conditions, which can enable substances to enter the brain.[57-60] In essence, targeted drug delivery mechanisms, including nanoparticles, may ultimately enhance the passage of substances across the BBB. Various instances of these carriers will be explored in the following sections.

Impact of Pharmacokinetic Principles on Drug Delivery to the Brain

Pharmacokinetic properties significantly influence the efficacy of systematically administered medications.[61] This journey from administration to the brain is fraught with challenges that often impede the effective delivery of therapeutic molecules. Notably, the presence of various plasma proteins can bind strongly to certain medications, reducing their circulation and the amount of free medication that can reach the brain.[62] Moreover, a significant portion of medications is rapidly eliminated by primary clearance organs, leaving only a small fraction in the bloodstream. Furthermore, the interaction of drugs with target cells can limit drug absorption, as these compounds can alter cell shape, membrane potential, or block channels, thereby influencing how the cell responds to the delivered drug molecule and how much of it is absorbed.[63] Typically, small lipophilic pharmacological molecules are more conducive to brain transport.[64]

Nanoparticles and Their Use in NDs

The unmet requirement for innovative therapeutic methods in addressing NDs stems from the limitations of the BBB and the limitations associated with current treatment options.[65] Emerging as nanotechnology reliable and efficient approach for targeted gene/drug delivery to the central nervous system, offering a promising solution.[66,67] Operating at the molecular level, this technique utilizes materials within the nanoscale range, typically spanning 1 to 1000 nm.[68] Nanoparticles can be engineered from various substances such as synthetic polymers (PCL and PLGA), inorganic minerals (silver, gold and cerium) and natural polymers (proteins and polysaccharides). Figure 1 illustrates the schematic illustration of different nanoparticles involved in the treatment of NDs. Studies have confirmed the efficacy of these nanocarriers as effective agents for transporting medication and genes to the brain.[69] Their significant benefits, such as their ability to carry a large drug payload, minimal risk of causing improved drug penetration, systemic toxicity and strong physical and chemical durability, position nanocarriers as a viable platform for the management and treatment of NDs (Figure 2).[66]

Inorganic Nanoparticles

Gold nanoparticles

Gold Nanoparticles (AuNPs) are extensively employed in theranostic applications because of their adaptability for surface modification, imaging and therapeutic purposes.[70] Studies have highlighted the unique capabilities of exosome-derived membranes and artificial AuNPs for targeted delivery to the brain. Notably, in experiments involving bioluminescence imaging, AuNPs coated with specific exosomes were observed to aggregate in the rat brain after intravenous injection. A creative and effective strategy for achieving precise brain targeting involves modifying the surfaces of synthesized AuNPs with brain-targeted exosomes.[71]

Amyloid diseases, such as Parkinson's and Alzheimer's, result from the creation of harmful intermediates during the self-assembly process within amyloidosis disorders. These disorders are connected to the misfolding of usually soluble and functional peptides and proteins, leading to the development of amyloid fibrils. Therefore, blocking, delaying, or disrupting the development of Aβ fibrils and oligomers is a major component of many AD therapies; in this regard, nanoparticles have shown notable impacts on the Aβ fibril formation process. However, research on their impact on the progression of cognitive decline and memory in living organisms has been limited. To explore how amyloid formation occurs, researchers utilized the α-lactalbumin protein as a suitable model due to its ability to enter a molten globule state. They discovered that in decreased α-lactalbumin, AuNPs suppress the formation of amyloid fibrils. More proteins adhering to the nanoparticle's surface and preventing structural alterations may be the cause of this protective effect. The nanoparticle prevents amyloid fibrils from combining and lengthening at their centre by attaching to the monomer. Consequently, it has the potential to be a potent therapeutic agent for addressing amyloid-related diseases and reducing amyloid production.[72]

Using AuNPs, such as AuNPs @POMD-pep (POMD: polyoxometalate with Wells-Dawson structure, pep: peptide), a multifunctional A inhibitor can be designed that improves the synergistic effects of reducing A-mediated peroxidase activity, dissociating A fibrils, preventing A aggregation and mitigating A-induced cytotoxicity.[73] Other studies suggest that the destructive Aβ aggregates can be targeted with the help of AuNPs conjugated to specific peptides. Conjugating AuNPs with the modified CLPFFD, beta-sheet breaker peptide, can effectively eradicate the harmful accumulations of Aβ peptides. Moreover, the addition of the THRPPMWSPVWP peptide sequence to the gold nanoparticle CLPFFD conjugate enhances its brain penetrability by interacting with the BBB's microvascular endothelial cells containing the transferrin receptor.[74] Moreover, AuNPs hinder the insulin fibrillogenic process. When insulin and AuNPs are co-incubated, the conversion of insulin fibrils into amyloid-like fibrils is postponed by a week. In addition, the resulting fibrils display modified characteristics in terms of dynamics, shape and structure, leading to a decrease in the fibril growth rate and the stability of the cross-β structured amyloid-like fibrils available for aggregation. AuNPs can interfere with insulin-induced amyloid fibrillation and also deter the creation of shorter, more condensed fibril variants. This characteristic of AuNPs may offer valuable insights into resolving issues related to diagnostic approaches for amyloid-associated diseases.[75] In rats that received Aβ treatment, it has been demonstrated that the use of AuNPs enhances their ability to learn and remember spatial information, both in terms of acquisition and retention. Moreover, the application of AuNPs increases the production of CREB, Brain-Derived Neurotrophic Factor (BDNF), Stromal Interaction Molecules (STIM1 and STIM2) and cAMP Response Element-Binding protein (CREB), all of which improve neuronal survival.[71] Electromagnetized gold nanoparticles enable direct lineage reprogramming for dopamine neuron growth in specific electromagnetic circumstances. Reprogramming dopaminergic neurons in PD models using EMF stimulation of AuNPs has shown encouraging outcomes in symptom reduction in a non-invasive way.[76] These new results imply that AuNPs may have a great deal of therapeutic promise in the field of molecular surgery for the treatment of depression that is not diagnostic.

Silver Nanoparticles

Following insertion into a living organism, Silver Nanoparticles (SNPs) traverse the bloodstream and eventually reach the brain. In a simulated scenario using microvascular endothelial cells derived from rat brain (referred to as BMVECs) in a model, the analysis of the distribution pattern of SNPs that traverse the BBB unveiled that, following a 4 hr Culturing in a solution with a concentration of 100 μg/mL of either SNPs or Silver Microparticles (SMPs), SNPs were capable of breaching the BBB and accumulating within BMVECs, whereas SMPs were not. Transcytosis of capillary endothelial cells seems to be the main way that SNPs cross the BBB.[77]

Similar observations on the BBB-penetration capacity of SNPs demonstrated that only SNPs and not SMPs, managed to penetrate the BBB and enter the brains of rats upon subcutaneous injection of both SNPs and SMPs (62.8 mg/kg). Upon direct injection into the brain, SNPs exhibited an ability to attach themselves to neurons, leading to an accumulation that triggered toxic effects, culminating in the destruction of neurons. The breakdown of neural cell membranes made it easier for the release of SNPs, impacting adjacent neurons, ultimately leading to the demise of cells and progressive changes in neural cells.

Notably, the disruption of the BBB utilizing the process of vascular endothelial cell transcytosis, which leads to the compromised integrity of tight junctions or dissolution of endothelial cell

membranes are plausible avenue through which SNPs gain access to the brain. Prolonged accumulation of SNPs in the brain may exacerbate neuronal necrosis and degeneration, particularly concerning solid core NPs that lack degradability.[78]

Innovatively devised nanoplatforms are designed as efficient delivery systems possessing distinctive nano-properties, aimed at regulating cell metabolism and intercellular communication. However, the immune system's oxidative modification of these novel components might yield unforeseen consequences, adversely affecting cellular functions. While the timely and efficient degradation of nanoscale drug carriers is imperative to their design, the rate of degradation of the nanocarrier relative to the drug payload necessitates careful calibration.[79]

It is imperative to consider the potential detrimental impacts of certain nanoparticles on metabolic pathways, along with identifying the underlying reasons for such effects. Reports indicate an increase in Amyloid Precursor Protein (APP) gene expression in brain cells treated with AgNPs. Neprilysin, a pivotal enzyme responsible for breaking down Aβ in the brain, as well as low-density lipoprotein receptors that assist in Aβ absorption and breakdown, showed decreased activity and lower protein levels in brain cells. Consequently, vigilance regarding the dispersion of AgNPs in the environment is crucial.[80]

Magnetic Nanomaterials

In various fields, including data storage, environmental remediation, biotechnology, biomedicine, MRI, magnetic fluids and catalysis, magnetic nanoparticles have attracted significant interest among researchers. Particularly in the realm of biomedicine, the application of Magnetic Nanoparticles (MNPs) has garnered increasing attention. Leveraging the unique characteristics of MNPs, such as their response to magnetic attraction, holds potential for enhancing drug targeting and cell sorting. A considerable body of research has explored the interplay between astrocytes and Iron Oxide Nanoparticles (IONPs).[81]

The concept of magnetic targeting revolves around the administration of drug-coated magnetic nanoparticles, guiding them to a specific site via regional variations in magnetic field strength, retaining them until the completion of treatment and subsequently extracting them. By minimizing the harmful effects and negative consequences arising from elevated drug levels in other body areas, magnetic drug carriers possess the capability to transport substantial medication doses, achieving elevated local concentrations.

Nevertheless, a crucial element in the creation and advancement of these nanoparticles for biomaterial-driven therapeutics lies in fine-tuning their dimensions. Previous research has predominantly focused on a limited range of IONP sizes. Recent advancements in micro/nanomotor technologies have led to the fabrication of magnetic micro/nanomotors utilizing innovative techniques such as glancing angle deposition, thin-film deposition, direct laser writing, spiral water conduction and membrane template-assisted electrodeposition. These micro/nanomotors are loaded with drugs to enhance drug concentration at the target site, regulate particle orientation and augment targeting efficiency. Furthermore, enhancing the Magnetic Field Strength (MFS) and nanoparticle diameter can amplify the magnetophoretic force and particle capture efficacy.

Comparative analysis between IONPs with diameters exceeding 300 nm and conventional nanoparticles with diameters below 100 nm revealed that IONPs exhibited higher retention and accumulation in tumours. One possible explanation for the prolonged presence of larger nanoparticles in tumours is the greater likelihood of smaller particles escaping the tumour due to their swifter traversal through blood vessels compared to larger counterparts.[82]

Clinical trials involving human patients with brain malignancies and prostate cancer have employed radiotherapy and local magnetic hyperthermia. Inducing heat through superparamagnetic particles in an alternating magnetic field has proven effective. Elevated temperatures reaching 42.5-43°C can temporarily reduce the activity of the BBB for 60 min, potentially enhancing the effectiveness of combined chemotherapies for brain cancers of particular promise are superparamagnetic Nanoparticles (NPs) equipped with Iron Oxide core (SPION) that can be targeted using external magnets. SPIONs can be functionalized with plasmids, proteins, or medications and coated with biocompatible materials. SPIONs functionalized with reversibly bound medications can be localized and administered to specific regions using an external magnetic field.[83]

Polymeric Nanomaterials

Polymers with sizes between one and 1000 nm are called "polymeric nanoparticles".[84] Degradable nanoparticles are the principal neurodegenerative drug carriers owing to their high drug loading capacity, low toxicity, customisable breakdown rates and ability to cross the BBB and reach the central nervous system.[85]

Use of biodegradable polymer nanoparticles improves the solubility, bioavailability and retention duration of numerous water-soluble/insoluble medications and bioactive compounds.[86] The biodegradability, biocompatibility, nontoxicity, non-immunogenicity and non-carcinogenicity of these polymeric systems are crucial for their usage in medicine and pharmaceuticals.[87] Medical and pharmaceutical applications employ Polylactic-Glycolic Acid (PLGA), Polyglycolic Acid (PGA) and Polylactic Acid (PLA).[88]

PLGA NPs may be created using a variety of formulation techniques, including top-down and bottom-up methods.

While unmodified PLGA NPs have several disadvantages, such as their non-BBB targeting, hydrophobic nature and negative charge, they also hold significant potential for drug delivery for CNS treatment. Recently, engineering methods have been able to address a few of these shortcomings. Polymer formation and hybridization of several techniques include core-shell encapsulation, cellular hybridization with PLGA, surface modification and attaching receptor-specific ligands to PLGA. The ability of PLGA NPs to pass the BBB, target specific tissues for encapsulated nucleic acids (siRNA) and deliver certain medications was enhanced by surface modification. Additionally, this tactic makes it easier for medications to be released gradually into their target areas.[89] Polysorbate 80 and polyaxmer 188 surface-coated PLGA-NPs demonstrated enhanced CNS penetration.[90] (531) PLGA is a biodegradable polymer that breaks down into lactic and glycolic acids and subsequently carbon dioxide thanks to the tricarboxylic acid cycle.[91] PLGA may result in homogeneous Nanoparticles (NPs) in a microemulsion. PLGA NPs encapsulated with antiviral nevirapine were shown to be permeable to Human Brain-Microvascular Endothelial cells (HBMECs), the primary biological component of the BBB, in research on medication delivery against the brain-dwelling human immunodeficiency virus. Furthermore, a synthetic cationic biopolymer with exceptional biocompatibility is polyacrylamide.[92] Polyacrylamide-cardiolipin-poly(lactide-co-glycolide) nanoparticles, featuring the grafting of the 83-14 monoclonal antibody on their surface were created by Kou and Tsai to carry curcumin and rosmarinic acid. Utilizing this medication delivery method allowed SK-N-MC cells (derived from human neuroblastoma) that had been damaged by β-Amyloid (Aβ) deposits to survive longer. Experimental data shows that an increased concentration of 83-14 MAb increases the permeability coefficient of rosmarinic acid and curcumin via the use of nanocarriers.[93] The Self-Micro-Emulsifying Drug Delivery System (SMEDDS) was used to manufacture an optimal paclitaxel microemulsion, allowing for a regulated release of the medication. This microemulsion contained poly (d,l-lactide-co-glycolide) and a combination of paclitaxel, tetra glycol, Cremophor ELP and Labrafil 1944 (PLGA). Paclitaxel demonstrated biphasic release features in microemulsions comprising PLGA with varying molecular weights (8K, 33K and 90K). Following an initial rapid release within the first 48 hr, the drug was progressively released over the subsequent 144 hr. However, paclitaxel became free from a microemulsion devoid of PLGA within a time frame of less than one day. Stelul-NP, an innovative biodegradable nasal-to-brain drug delivery system, is composed of conjugated Poly (DL-Lactic-co-Glycolic Acid) (PLGA) nanoparticles of Solanum Tuberosum Lectin (STL). The efficacy of STL-NP in targeting various brain tissues was found to be 1.89-2.45 times greater than that of unmodified NP.[94] In a BBB model, siRNA-chitosan nanoparticles have been shown to significantly reduce the activity of the P-glycoprotein (P-gp) gene. The knockdown led to a significant decrease in P-gp substrate efflux and enhanced doxorubicin delivery, which might be used as a model.

The size-dependent BBB penetration of PLA-NPs preloaded with the flavonoid breviscapine was observed; bigger particles (~300 nm) delivered higher drug concentrations in the brain in comparison to smaller nanoparticles (approximately 200 nm). On the other hand, by eluding efflux transporters, the PLA-NP surface-associated Trans-Activating Transcriptor (TAT) peptide induced an increase in the NPs' transit across the BBB. These findings suggest that using nanoparticles to deliver anti-P-gp siRNA may be a useful tactic to improve the treatment of a number of CNS illnesses where the BBB presently prevents drug administration from occurring.[95]

Carbon Nanomaterials

Owing to their distinctive blend of chemical and physical attributes, including electrical conductivity and thermal, strength, obust mechanical and optical properties, nanomaterials composed of carbon and featuring water-repellent surfaces, like the spherical fullerene (C60), elongated Carbon Nanotubes (CNTs) and flat two-dimensional graphene, have attracted significant attention in the field of medical nanotechnology.[96] Subsequently, this section will explore several applications for these nanomaterials.

Graphene

Due to their beneficial characteristics, graphene and Graphene Oxide (GO) have become innovative and competitive technology for drug delivery. In addition to focused systemic medication administration, they may find use in localised drug delivery systems.[97] Graphene-based materials frequently undergo assembly in an aqueous medium that comprises proteins, salts, or other ions in order to attain the intended characteristics. This process, known as chemical modification or functionalization, allows researchers to manipulate graphene's fundamental electrical and optical characteristics, facilitating the attachment of medications, genes, ligands, peptides, antibodies and contrast agents to the graphene nanoparticle surface.[98]

Layer-by-layer deposition was utilized to create graphene-heparin/poly-L-lysine polyelectrolyte coatings on both 2D substrates and 3D electro-spun nanofibers. In cell culture experiments, graphene-PEMs in both 2D and 3D configurations sustained neurite development and neuron cell adhesion, demonstrating no apparent cell death. Consequently, this modification of the electroactive scaffold holds promise in aiding neural regeneration and producing biocompatible and functional polymer scaffolds for biosensing or electrical entrainment applications.[99]

To promote the restoration of neurons and improve functional recovery following a brain injury, utilizing electroactive methods can be highly beneficial in exploring various materials next-generation scaffolds for neural tissue engineering have

undergone thorough examination. *In vitro* studies on the survival and development of neuronal cells have yielded encouraging results for graphene, a newly developed neural scaffold material endowed with charge transfer capabilities.[100]

Fullerenes

Fullerenes protect two primary mechanisms: their hydrophobic surface and their radical sponge attribute. The unique structure of fullerene includes a "radical sponge," capable of entrapping numerous radicals within a single molecule sphere, thereby exhibiting potent antioxidant properties against cytotoxicity arising from intracellular oxidative stress.[101] Researchers have explored the protective properties of $C_{60}(OH)_{24}$, a polyhydroxylated fullerene derivative, in a cellular model of acute PD induced by 1-Methyl-4-Phenylpyridinium (MPP1) using human neuroblastoma cells. The findings indicate that C60(OH)24 exhibits substantial antioxidant qualities, effectively safeguarding mitochondria and effectively scavenging free radicals. This suggests its promising potential as a preventive strategy against mitochondrial impairment and oxidative stress in MPP1-treated cells.

In a distinct investigation, researchers synthesized water-soluble derivatives of C60 fullerene. These derivatives exhibited various types of chemical bonds: compounds 1-3 featured C-C connections, compounds 4-5 contained C-S bonds, compound 6 incorporated C-P bonds and compounds 7-9 displayed C-N bonds, among other connections between the fullerene structure and the solubilizing component. According to the research, fullerene derivatives 1-6 could improve Neural Stem Cell (NSC) proliferation *in vitro* and restore normal function to zebrafish with injured central nervous systems. Furthermore, fullerene derivatives 7-9 could prevent the growth of glioma cells *in vitro* as well as the formation of glioblastoma in zebrafish. These effects were linked to alterations in cell metabolism. Notably, compound 3 containing phenylbutyric acid residues significantly enhanced neural repair and NSC proliferation without promoting tumor formation. Conversely, compound 7 containing phenylalanine appendages notably impeded the formation of glioblastomas without impeding neural healing. The specific surface functional group of C60 governs its characteristics and interactions with NSCs and glioma cells, potentially leading to either an anticancer or neuroprotective impact for the treatment of CNS-related disorders, including the cellular model of PD.[102]

Carbon Nanotubes

Allotropes of carbon with a cylindrical nanostructure are called carbon nanotubes. Single-atom-thick sheets make form the longitudinal, void-like structures of nanotubes and other fullerene family members. These carbon nanotubes, which consist of one or more carbon layers, are categorised as single-wall and multi-wall CNTs.[103,104] These carbon-based nanoparticles find utility in medicine[105] due to their distinctive mechanical, chemical and electrical characteristics.[106] CNTs, both in their pure form and when modified by various polymers, have been under scrutiny. The creation of hybrid nanotube-neuron networks has the potential to enhance synaptic development, network communication and neuronal activity. With their extraordinary physical attributes and newly discovered capability to interact with synapses, neural circuits and membranes, CNT-based technologies hold promises for facilitating the neuronal recovery of function after a brain injury.

Through electron microscopy analysis, theoretical modelling and single-cell electrophysiology techniques, Cellote *et al.* discovered that nanotubes enhance neuronal responsiveness by establishing and facilitating direct connections with cellular membranes, enabling the establishment of electrical pathways between the adjacent and distant sections of the neuron.[107] Neurotrophin-coated multi-walled CNTs were utilized to regulate neuronal survival and differentiation. The Enzyme-Linked Immunosorbent Assay (ELISA) was utilized to establish that CNTs coated with neurotrophins act as carriers for these neurotrophic factors. These results imply that these neurotrophin-coated CNTs could potentially display biological effects, facilitating the growth of neuronal extensions known as neuritis.[108] Moreover, maintaining of the association between Carbon-based Nanoparticles (CNTs) and stem cells offers an innovative outlook on the potential application of these nanoparticles in cellular simulation-based nervous tissue generation and modeling.[109]

Strategies to Overcome Drug Delivery Impediments

Extensive clinical studies have shown significant deficits in the cholinergic-neurotransmitter systems of Alzheimer's patients, which may be related to the inhibition of acetylcholine by Acetylcholinesterase (AChE) activity, which is essential for brain connections.[110] Notably, increasing evidence indicates that a key factor in the pathophysiology of AD is the activation of the glutamatergic system.[111,112] A few of authorised drug candidates have been developed as a result of these groundbreaking discoveries, most notably the NMDA inhibitor galantamine, the AChE inhibitor galantamine, donepezil, rivastigmine and tacrine.[113]

The efficient delivery of these medications to the specific brain cells is, as stated previously, hindered by a few substantial obstacles. Thus, advancements in the domain of nanotechnology have been concentrated on the development of nanomaterials that have the capability to augment the transportation of active pharmaceutical candidates. This presents a prospective resolution to the difficulties. Through surface modification, nanoparticles have emerged as potentially effective agents that can traverse the BBB and enable improved delivery of drugs to the brain. Teleanu *et al.* (2019) have brought attention to the increasing importance of neuronanomedicine, an emerging interdisciplinary domain that combines nanotechnology and neurological science. This

discipline exhibits potential for both diagnosing and treating disorders of the CNS.[114]

Among the early successes in this field, the utilization of poly (butyl cyanoacrylate) nanoparticles coated in polysorbate enabled the BBB penetration of Dalargin, a hexapeptide, marking a significant milestone in drug delivery.[83] In the subsequent discussion, we will delve into a few of these pioneering strategies.

Enhancing Local Drug Delivery

Diverse treatment techniques and extensive research on local drug delivery systems in the CNS[115] have resulted from endeavours to enhance the delivery of nanodrugs to their intended targets, which are predominantly situated in the CNS. Achieving high doses of medication over an extended duration through the application of polymer pellets to the brain is contingent upon the local rates of drug transit and clearance from brain tissues. The constrained penetration of drugs released from implants across tumour margins significantly diminishes therapeutic effectiveness, despite the potential for delivering an increased drug dose to the tumour resection.[115] Consequently, researchers have sought alternative chemotherapy drugs capable of penetrating brain cells and surrounding tissues based on their physical properties. Liposomal nanoparticles have gained attention recently as a potential local medication delivery method to the central nervous system.[116,117] Previously, the main issue with local delivery methods was the use of large microparticles, such as polymer microspheres of chitosan, Poly (Methylidene Malonate) (PMM), PLGA and poly (epsilon-caprolactone).[118] While these polymers hold promise for treating various brain disorders, their size and surface characteristics hinder effective transportation. Designing, microfluidic probes enable the expansion of the brain's extracellular matrix's effective pore size. Intracranial infusion, also known as convection-enhanced delivery, or CED, has gained popularity recently. Rather than depending only on bigger microparticles (ECM) for drug administration, it allows the introduction of proteins and other particles, including polymeric and liposomes nanoparticles smaller than 100 nm.[119] Two methods have been used to improve injected nanoparticle transport: enzymatic digestion of specific ECM components and ECM dilation. Their findings suggest that this approach could improve the passage of nanoparticles into the brain parenchyma. Notably, the transport of polymeric nanoparticles is greatly facilitated by extracellular space dilation and enzymatic treatment.[119] CED proves to be a valuable method for gene therapy applications by infusing the bio-organism into different brain regions, delivering large chemicals and particles to the CNS, or transducing broad portions of the cortex.[120,121] Compared to traditional diffusion-based injections, Greater benefits may be obtained with CED in terms of more uniform vector densities throughout the expressing areas, allowing the infusion of substantial volumes of vectors over a short period through a single infusion site.[120,122] Because MRI requires fewer injections and infuses viral vector more quickly, it also permits accurate targeting and real-time monitoring throughout the preparation and infusion of the vector.[122]

Leveraging Receptor-Mediated Transcytosis

The receptor-mediated transcytosis pathway is of critical importance in the transportation of a variety of endogenous macromolecules to the brain. This process utilises BBB cells with highly expressed receptors to facilitate the transport of functionalized nanomaterial across the BBB endothelium. Most nanoparticles require receptor-mediated transcytosis to effectively cross the BBB.[123] If surface-engineered to utilize BBB transport pathways, these nanocarriers can effectively target the brain, with up to 0.1-1% of the injected dose reaching the brain without this modification. Among various nanoparticle engineering strategies, the ligand-based approach has emerged as a compelling method for achieving more targeted and specific medication administration to the central nervous system. This approach entails modifying nanoparticles by attaching various ligands, such as lactoferrin, transferrin, insulin and surfactants like polysorbate.[83,123] The formation of vesicles via the endocytosis pathway is induced by the conduction of the plasma membrane triggered by the interaction of ligand-bound nanoparticles with brain endothelial cells. Following the release of the ligands from these vesicles, the nanoparticles can cross the BBB through the process of exocytosis. This allows them to carry out their designated function within the brain parenchyma without posing a threat to the integrity of the BBB.[124,125] Further elucidating the mechanisms underlying the upregulation of diverse receptors and receptor-mediated BBB traversal may be regarded as a potentially fruitful technical instrument in the realm of neurological drug delivery. Interleukin 13 receptors, insulin receptors, lipoprotein receptors, transferrin receptors and lactoferrin receptors are all noteworthy instances of receptor-ligand systems.[126]

Manipulating BBB through Physicochemical Means

The strategies currently used in nanotechnology hold out hope for manipulating and disturbing the BBB, such as magnetic disruption, cell-penetrating peptides and magnetic resonance imaging-ultrasound technology.[127]

Magnetic Resonance Imaging-Ultrasound (MRI-US)

Magnetic Resonance Imaging (MRI), a crucial technique in clinical imaging for brain disease detection, offers excellent resolution in both time and space. Advances in nanotechnology have led to the creation of nanoplatforms aimed at improving the delivery of contrast agents through MRI. Researchers have developed a biodegradable nanoparticle-based technology to facilitate the precise scanning of molecular imaging probes that cannot easily cross the BBB into the brain. The delivery of MRI contrast agents to the brain is greatly improved by coating them with nanoparticles. Active medication delivery and imaging

systems that react to external stimuli including pH, magnetic fields and focused ultrasound are also available. Notably, a pH-sensitive nano platform has recently been introduced as a safe and effective method for delivering chemotherapy systemically while enabling dual-mode MRI for tumor targeting, with no adverse side effects.[128]

When combined with circulating microbubbles, focused ultrasound can breach the BBB temporarily and safely, allowing immunotherapeutic medications to be delivered into the brain parenchyma.[129] This non-invasive technique, typically performed with MRI or diagnostic ultrasound under real-time image guidance, significantly enhances the administration and distribution of therapeutic drugs and genes, as well as strengthening tissue immune responses.[130,131] Ultrasound-based methods utilize the energy produced by acoustically generated microbubbles to temporarily and reversibly enhance the permeability of vascular endothelium. This in turn makes it possible for certain molecules to pass across the BBB and enter the central nervous system.[117,131]

The application of MRI-guided Focused Ultrasound (MRIgFUS) has proven effective in reducing plaque pathology by delivering anti-Ab antibodies. Intravenously administered anti-Ab antibodies can penetrate brain regions targeted by FUS, as demonstrated in an alternative mouse model of Alzheimer's disease (B6C3-Tg).[132,133] The BBB's restrictions on the efficient treatment of Nerve Diseases (NDs) may be circumvented by combining MRIgFUS with microbubbles to enable the localised, non-invasive release of neurotrophic factors like Glial cell line-Derived Neurotrophic Factor (GDNF) into the CNS.[134] The efficacy of delivering large macromolecules, small compounds and even nanoparticles to the brain may be improved by using methods to momentarily alter BBB permeability.

Cell Penetrating Peptides (CPP)

CPPs constitute a varied group of short peptides abundant in cationic amino acids like arginine and lysine, which are capable of efficiently penetrating the BBB with drugs.[135-138] They aid in the delivery of siRNA, proteins and small molecular drugs, penetrating biomaterials into cell membranes in a ubiquitous manner.[115,137,139,140] While positively charged peptides make up the majority of CPPs, it has been demonstrated that some anionic and hydrophobic CPPs also exist. Peptides produced from proteins, chimeric peptides made by fusing two natural sequences and synthetic CPPs based on structure-activity investigations are the three main types of CPPs.[140] Although the specific mechanism of CPPs' cell membrane penetration is yet unclear, the transport of nanomaterials modified with CPPs across the BBB is made possible by the interaction of positively charged charges in CPPs with the surfaces of brain endothelial cell membranes via electrostatic forces.[115] Contrary to previous assumptions suggesting only direct translocation, recent evidence supports the widely acknowledged mechanisms of endocytosis and direct translocation in facilitating CPPs' membrane penetration.[141] However, the non-specific affinity of CPP-mediated brain delivery systems to various cells results in a high distribution of drugs across the entire brain, potentially leading to unintended toxicity in normal brain structures.[138] To address this issue, a brain drug delivery system based on transferrin and CPP dual-functioned liposomes (Tf/TAT-lip) has been developed for glioma treatment. *In vitro* tests have shown that Tf/TAT co-modified liposomes effectively transport medicinal substances across the BBB and ex vivo biodistribution studies have confirmed improved permeability into parenchymal cells.[137] Another successful method for improving the penetration of nanoparticles into the brain through the Tf receptor-mediated pathway involves the addition of a secondary ligand to enhance cellular entry. In experiments conducted in living organisms, employing a dual-ligand strategy has shown an elevation in the number of liposomes that manage to reach the brain and *in vitro* tests have confirmed improved permeability into parenchymal cells.[142] Through the use of magnetic guidance and TAT conjugation, Magnetic Poly Lipid nanoparticles (MPLs) have been engineered to precisely target the brain. This has resulted in effective drug delivery to brain parenchymal cells, exhibiting intense fluorescence in both the cytoplasm and cell nucleus.[143] This strategy shows promise as a successful means of delivering medication across the BBB.

Magnetic Disruption

Nanoparticles can produce heat or hyperthermia when exposed to an alternating magnetic field, which speeds up the transit rates of nanoparticle ferrofluids.[117] This heat may thermally destroy a BBB that is still intact within the brain's microvasculature, providing a brief window of opportunity for therapeutic substances to enter brain tissue. It is well recognized that prolonged exposure to heat may result in significant cellular stress and temporal disruption of the BBB.[144] The most popular methods for breaking through the BBB among the several types of hyperthermia are microwave, radiofrequency and whole-body hyperthermia.[144,145] Increasing the body temperature of the brain in its whole, including that of its neurons, astrocytes, blood vessel wall cells and other glial cells, is frequent among these techniques. This strategy might hurt the BBB and have very negative consequences. Conversely, thermal conduction causes only the blood vessel wall cells situated near Magnetic Nanoparticles (MNPs) that have been triggered in an alternating magnetic field to heat up. But because of the induced hyperthermia, this leads to the breakdown of the BBB.[145] Thus, the only tissues that are directly affected by heat stress are the endothelial cells and the monolayer lining of the vessel walls. Furthermore, the combination of targeted ultrasound and magnetic disruption may enhance the BBB transportability of therapeutic magnetic nanoparticles.[146] It has been shown that N (trimethoxysilylpropyl) Ethylenediamine Triacetate [EDT]-iron

oxide nanoparticles display improved bulk flow permeability across brain micro vessel endothelial cells that are briefly damaged, while having no impact on Magnetic Field Enhanced Convective Diffusion (MFECD). A higher delivery efficiency was seen when MFECD of EDT-IONPs was contrasted with passive or active targeting of BBB vesicular transport channels.[147] Using hollow MNPs, which allow for the loading of pharmaceuticals both on the surface and within their hollow core,[148] could be a solution to the current limitation of insufficient payload capacity in MNPs,[149] where pharmaceuticals can only be embedded to the surface or within the double-layer coating enveloping the MNPs.

Prospects and Challenges

Over the last few decades, extensive research efforts have been dedicated to NDs, both in preclinical and clinical settings. However, the effectiveness of medications has been limited due to the BBB. NDs could potentially benefit from the use of Novel Drug Delivery Systems (NDDSs) as they enhance drug delivery to the brain. Despite this potential, the clinical market has yet to witness the success of any therapeutic nanotherapeutic. Consequently, comprehensive investigations are necessary to tackle safety and biocompatibility issues, along with concerns regarding interactions with the biological environment and regulatory demands, to facilitate the translation of nanotherapeutics from preclinical research to clinical application. Nanomaterials can easily get through the BBB and reach the right part of a person with ND's brain. Because of this, these nanosized vehicles may show that they have better therapeutic results (Figure 3).

Before commencing clinical trials, several crucial issues and challenges must be addressed. Firstly, an evaluation of the safety of prolonged use is essential. Due to the distinctive features of nanomedicines, conventional toxicological assessments often fail to provide a reliable understanding of their safety. Moreover, there remains a lack of clinical and *in vivo* data on the neurotoxicity of NDDSs, especially concerning older adults whose brain homeostasis capabilities are diminished.[150] In-depth research is necessary to determine the precise localization of these NDDSs in the brain. Common delivery routes for Nanoparticles (NPs) include nasal, oral and intravenous administration.[151] To improve their delivery efficiency over the BBB and into the brain, NDDSs and existing technologies must be further improved. Non-primate animal models, which have poor dependability, make up the bulk of the models used in these investigations.[152] Appropriate safety evaluations of nanomedicines must be developed in order to get a thorough knowledge of the processes and targeting of different drug delivery pathways to the central nervous system. Moreover, more preclinical studies using monkey models are required to expedite the introduction of more nanomedicines into clinical settings.

CONCLUSION

The BBB is vital for central nervous system function, but its disruption contributes to brain pathologies. Understanding BBB regulation is essential for comprehending disease mechanisms. While the causes of BBB dysfunction are not fully understood, advances in understanding physical and molecular changes during breakdown offer opportunities for innovative drug delivery, notably through nanomaterial. Tailoring nanomaterial with surface ligands, density and shape can enhance drug transport across the BBB. Promising findings in animal models of neurological diseases raise the prospect of clinical trials. Ensuring the safety of medication delivery to the brain and specifically targeting particular cells such as dopaminergic neurons or microglia brings up new possibilities for regenerative medicine. Exploiting BBB changes alongside innovative agents promises more effective and non-invasive brain therapies, potentially revolutionizing brain pathology treatment and improving patient quality of life.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NDs: Neurodegenerative Diseases; **AD:** Alzheimer's disease; **HD:** Huntington's Disease; **PD:** Parkinson's Disease; **ALS:** Amyotrophic Lateral Sclerosis; **FTD:** Frontotemporal Dementia; **SCAs:** Spinocerebellar ataxias; **PSP:** Progressive supranuclear palsy; **NMDA:** N-methyl-D-aspartate; **COMT:** Catechol-O-methyl transferase; **NMS:** Non-motor symptoms; **BBB:** Blood-Brain Barrier; **GLUT-1:** Glucose Transporter-1; **BDNF:** Brain-Derived Neurotrophic Factor; **STIM:** Stromal Interaction Molecules; **SNPs:** Silver Nanoparticles; **APP:** Amyloid Precursor Protein; **MNPs:** Magnetic Nanoparticles; **IONPs:** Iron Oxide Nanoparticles; **MFS:** Magnetic Field Strength; PL**GA:** Polylactic-glycolic Acid; **PGA:** Polyglycolic Acid; **PLA:** Polylactic Acid; **STL:** *Solanum Tuberosum* Lectin; **TAT:** Trans-Activating Transcriptor; **CNTs:** Carbon Nanotubes; **NSC:** Neural Stem Cell; E**LISA:** Enzyme-Linked Immunosorbent Assay; **CNTs:** Carbon-based Nanoparticles; **AChE:** Acetylcholinesterase.

SUMMARY

The Blood-Brain Barrier (BBB) is crucial for central nervous system function and disruptions contribute to various brain pathologies. Though the exact causes of BBB dysfunction are not fully understood, advancements in understanding its physical and molecular changes offer opportunities for innovative

drug delivery, especially through nanomaterial. Customizing nanomaterial characteristics can enhance drug transport across the BBB, with promising results in animal models suggesting potential clinical trials. Safely delivering medication to the brain and targeting specific cell types opens new possibilities in regenerative medicine. Exploiting BBB changes alongside innovative agents holds promise for more effective and non-invasive brain therapies, potentially revolutionizing the treatment of brain pathologies and improving patient quality of life.

REFERENCES

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abdelalim A, Abdollahi M. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The lancet. 2020;396(10258):1204-22.
2. Terreros-Roncal J, Moreno-Jiménez EP, Flor-García M, Rodríguez-Moreno CB, Trinchero MF, Cafini F, Rábano A, Llorens-Martín M. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science. 2021;374(6571):1106-13.
3. Hansson O. Biomarkers for neurodegenerative diseases. Nature medicine. 2021;27(6):954-63.
4. Scheltens P, Blennow K, Breteler MM, De Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. The Lancet. 2016;388(10043):505-17.
5. Sengupta U, Kayed R. Amyloid β, Tau, and α-Synuclein aggregates in the pathogenesis, prognosis, and therapeutics for neurodegenerative diseases. Progress in neurobiology. 2022;214:102270.
6. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. Immunology. 2018;154(2):204-19.
7. Cenini G, Lloret A, Cascella R. Oxidative stress and mitochondrial damage in neurodegenerative diseases: from molecular mechanisms to targeted therapies. Oxidative medicine and cellular longevity. 2020; 2020.
8. Janicki Hsieh S, Alexopoulou Z, Mehrotra N, Struyk A, Stoch SA. Neurodegenerative diseases: The value of early predictive end points. Clinical Pharmacology and Therapeutics. 2022;111(4):835-9.
9. Segarra M, Aburto MR, Acker-Palmer A. Blood-brain barrier dynamics to maintain brain homeostasis. Trends in neurosciences. 2021;44(5):393-405.
10. Terstappen GC, Meyer AH, Bell RD, Zhang W. Strategies for delivering therapeutics across the blood-brain barrier. Nature Reviews Drug Discovery. 2021;20(5):362-83.
11. Song F, Li X, Wang Q, Liao L, Zhang C. Nanocomposite hydrogels and their applications in drug delivery and tissue engineering. Journal of biomedical nanotechnology. 2015;11(1):40-52.
12. An N, Liu S, Fang C, Yu R, Zhou X, Cheng Y. Preparation and properties of β-phase graphene oxide/PVDF composite films. Journal of Applied Polymer Science. 2015;132(10).
13. Peng H, Liu X, Wang R, Jia F, Dong L, Wang Q. Emerging nanostructured materials for musculoskeletal tissue engineering. Journal of Materials Chemistry B. 2014;2(38):6435-61.
14. Lu Y, Li X, Zhou X, Wang Q, Shi X, Du Y, Deng H, Jiang L. Characterization and cytotoxicity study of nanofibrous mats incorporating rectorite and carbon nanotubes. RSC advances. 2014;4(63):33355-61.
15. Liu M, Li M, Wang G, Liu X, Liu D, Peng H, Wang Q. Heart-targeted nanoscale drug delivery systems. Journal of biomedical nanotechnology. 2014;10(9):2038-62.
16. Li W, Li X, Wang Q, Pan Y, Wang T, Wang H, Song R, Deng H. Antibacterial activity of nanofibrous mats coated with lysozyme-layered silicate composites via electrospraying. Carbohydrate polymers. 2014;99:218-25.
17. Xin S, Li X, Wang Q, Huang R, Xu X, Lei Z, Deng H. Novel layer-by-layer structured nanofibrous mats coated by protein films for dermal regeneration. Journal of biomedical nanotechnology. 2014;10(5):803-10.
18. Mignani S, Bryszewska M, Zablocka M, Klajnert-Maculewicz B, Cladera J, Shcharbin D, Majoral JP. Can dendrimer based nanoparticles fight neurodegenerative diseases? Current situation versus other established approaches. Progress in Polymer Science. 2017;64:23-51.
19. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. Cold Spring Harbor perspectives in biology. 2017; 9(7):a028035.
20. Ahmed MQ, Alenazi FS, Fazaludeen MF, Shahid SM, Kausar MA. Pathology and Management of Alzheimer's disease: A review. International journal of pharmaceutical research and allied sciences. 2018;7(2).
21. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. Jama. 2020;323(6):548-60.
22. Stoker TB, Mason SL, Greenland JC, Holden ST, Santini H, Barker RA. Huntington's disease: Diagnosis and management. Practical neurology. 2022;22(1):32-41.
23. Morris J. Amyotrophic lateral sclerosis (ALS) and related motor neuron diseases: an overview. The Neurodiagnostic Journal. 2015;55(3):180-94.
24. Joy JE, Johnston Jr RB. Future Strategies for MS Therapies. InMultiple Sclerosis: Current Status and Strategies for the Future 2001. National Academies Press (US).
25. Weder ND, Aziz R, Wilkins K, Tampi RR. Frontotemporal dementias: a review. Annals of general psychiatry. 2007;6(1):1-0.
26. Ironside JW, Ritchie DL, Head MW. Prion diseases. Handbook of clinical neurology. 2018;145:393-403.
27. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nature reviews Disease primers. 2019;5(1):24.
28. Giagkou N, Höglinger GU, Stamelou M. Progressive supranuclear palsy. International review of neurobiology. 2019;149:49-86.
29. Dunn B, Stein P, Cavazzoni P. Approval of aducanumab for Alzheimer disease—the FDA's perspective. JAMA internal medicine. 2021;181(10):1276-8.
30. Walsh S, Merrick R, Milne R, Brayne C. Aducanumab for Alzheimer's disease? bmj. 2021;374.
31. Wu KM, Zhang YR, Huang YY, Dong Q, Tan L, Yu JT. The role of the immune system in Alzheimer's disease. Ageing research reviews. 2021;70:101409.
32. Hampel H, Mesulam MM, Cuello AC, Khachaturian AS, Vergallo A, Farlow MR, *et al*, Cholinergic System Working Group and for the Alzheimer Precision Medicine Initiative (APMI). Revisiting the cholinergic hypothesis in Alzheimer's disease: emerging evidence from translational and clinical research. The journal of prevention of Alzheimer's disease. 2019;6:2-15.
33. Deardorff WJ, Feen E, Grossberg GT. The use of cholinesterase inhibitors across all stages of Alzheimer's disease. Drugs and aging. 2015;32:537-47.
34. Liu PP, Xie Y, Meng XY, Kang JS. History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal transduction and targeted therapy. 2019;4(1):29.
35. Johnson JW, Kotermanski SE. Mechanism of action of memantine. Current opinion in pharmacology. 2006;6(1):61-7.
36. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine. 2003;348(14):1333-41.
37. Folch J, Busquets O, Ettcheto M, Sánchez-López E, Castro-Torres RD, Verdaguer E, *et al.* Memantine for the treatment of dementia: a review on its current and future applications. Journal of Alzheimer's Disease. 2018;62(3):1223-40.
38. Emamzadeh FN, Surguchov A. Parkinson's disease: biomarkers, treatment and risk factors. Frontiers in neuroscience. 2018;12:612.
39. Alexander GC, Knopman DS, Emerson SS, Ovbiagele B, Kryscio RJ, Perlmutter JS, *et al.* Revisiting FDA approval of aducanumab. New England Journal of Medicine. 2021;385(9):769-71.
40. Tripathi A, Gupta PK, Bansal T. Management of Psychiatric Disorders in Patients with Parkinson's Diseases. Indian Journal of Psychiatry. 2022;64(S2):S330.
41. Bucchia M, Ramirez A, Parente V, Simone C, Nizzardo M, Magri F, *et al.* Therapeutic development in amyotrophic lateral sclerosis. Clinical therapeutics. 2015;37(3):668-80.
42. Jaiswal MK. Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. Medicinal Research Reviews. 2019;39(2):733-48.
43. Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation and clinical implications. Neurobiology of disease. 2004;16(1):1-3.
44. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harbor perspectives in biology. 2015; 7(1):a020412.
45. Felgenhauer K. Protein size and cerebrospinal fluid composition. Klinische Wochenschrift. 1974;52(24):1158-64.
46. Greene C, Campbell M. Tight junction modulation of the blood brain barrier: CNS delivery of small molecules. Tissue barriers. 2016;4(1):e1138017.
47. Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. Pharmacological reviews. 2005;57(2):173-85.
48. Nakagawa S, Deli MA, Kawaguchi H, Shimizudani T, Shimono T, Kittel A, Tanaka K, Niwa M. A new blood-brain barrier model using primary rat brain endothelial cells, pericytes and astrocytes. Neurochemistry international. 2009;54(3-4):253-63.
49. Serlin Y, Shelef I, Knyazer B, Friedman A. Anatomy and physiology of the blood-brain barrier. In Seminars in cell and developmental biology 2015;38:2-6. Academic Press.
50. Begley DJ. ABC transporters and the blood-brain barrier. Current pharmaceutical design. 2004;10(12):1295-312.
51. Hladky SB, Barrand MA. Elimination of substances from the brain parenchyma: efflux via perivascular pathways and via the blood-brain barrier. Fluids and Barriers of the CNS. 2018;15(1):1-73.
52. Lockman PR, Mumper RJ, Khan MA, Allen DD. Nanoparticle technology for drug delivery across the blood-brain barrier. Drug development and industrial pharmacy. 2002;28(1):1-3.
53. van de Waterbeemd H, Camenisch G, Folkers G, Chretien JR, Raevsky OA. Estimation of blood-brain barrier crossing of drugs using molecular size and shape and H-bonding descriptors. Journal of drug targeting. 1998 Jan 1 ; 6(2):151-65.
54. Di L, Artursson P, Avdeef A, Ecker GF, Faller B, Fischer H, *et al.* Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. Drug discovery today. 2012;17(15-16):905-12.

55. Fischer H, Gottschlich R, Seelig A. Blood-brain barrier permeation: molecular parameters governing passive diffusion. The Journal of membrane biology. 1998;165:201-11.
56. Arora S, Sharma D, Singh J. GLUT-1: An effective target to deliver brain-derived neurotrophic factor gene across the blood brain barrier. ACS chemical neuroscience. 2020;11(11):1620-33.
57. Lee H, Pienaar IS. Disruption of the blood-brain barrier in Parkinson's disease: curse or route to a cure? Frontiers in Bioscience-Landmark. 2014;19(2):272-80.
58. Kook SY, Hong HS, Moon M, Mook-Jung I. Disruption of blood-brain barrier in Alzheimer disease pathogenesis. Tissue Barriers 1, e23993.
59. Argaw AT, Asp L, Zhang J, Navrazhina K, Pham T, Mariani JN, *et al.* Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. The Journal of clinical investigation. 2012;122(7):2454-68.
60. Sengillo JD, Winkler EA, Walker CT, Sullivan JS, Johnson M, Zlokovic BV. Deficiency in Mural Vascular Cells Coincides with Blood-Brain Barrier Disruption in A lzheimer's Disease. Brain pathology. 2013;23(3):303-10.
61. Dong X. Current strategies for brain drug delivery. Theranostics. 2018;8(6):1481.
62. Ghuman J, Zunszain PA, Petitpas I, Bhattacharya AA, Otagiri M, Curry S. Structural basis of the drug-binding specificity of human serum albumin. Journal of molecular biology. 2005;353(1):38-52.
63. Krol S. Challenges in drug delivery to the brain: nature is against us. Journal of Controlled Release. 2012;164(2):145-55.
64. Pardridge WM. Drug transport across the blood-brain barrier. Journal of cerebral blood flow and metabolism. 2012;32(11):1959-72.
65. Teleanu DM, Negut I, Grumezescu V, Grumezescu AM, Teleanu RI. Nanomaterials for drug delivery to the central nervous system. Nanomaterials. 2019;9(3):371.
66. Poovaiah N, Davoudi Z, Peng H, Schlichtmann B, Mallapragada S, Narasimhan B, *et al.* Treatment of neurodegenerative disorders through the blood-brain barrier using nanocarriers. Nanoscale. 2018;10(36):16962-83.
67. Chauhan PS, Yadav D, Koul B, Mohanta YK, Jin JO. Recent advances in nanotechnology: a novel therapeutic system for the treatment of Alzheimer's disease. Current Drug Metabolism. 2020;21(14):1144-51.
68. Spuch C, Saida O, Navarro C. Advances in the treatment of neurodegenerative disorders employing nanoparticles. Recent patents on drug delivery and formulation. 2012;6(1):2-18.
69. Modi G, Pillay V, Choonara YE. Advances in the treatment of neurodegenerative disorders employing nanotechnology. Annals of the New York Academy of Sciences. 2010;1184(1):154-72.
70. Ajnai G, Chiu A, Kan T, Cheng CC, Tsai TH, Chang J. Trends of gold nanoparticle-based drug delivery system in cancer therapy. Journal of Experimental and Clinical Medicine. 2014;6(6):172-8.
71. Sanati M, Khodagholi F, Aminyavari S, Ghasemi F, Gholami M, Kebriaeezadeh A, *et al.* Impact of gold nanoparticles on amyloid β-induced AD in a rat animal model: Involvement of STIM proteins. ACS chemical neuroscience. 2019;10(5):2299-309.
72. Talebpour F, Ghahghaei A. Effect of green synthesis of gold nanoparticles (AuNPs) from Hibiscus sabdariffa on the aggregation of α-lactalbumin. International Journal of Peptide Research and Therapeutics. 2020;26:2297-306.
73. Gao N, Sun H, Dong K, Ren J, Qu X. Gold-Nanoparticle-Based Multifunctional Amyloid-β Inhibitor against Alzheimer's Disease. Chemistry-A European Journal. 2015;21(2):829-35.
74. Prades R, Guerrero S, Araya E, Molina C, Salas E, Zurita E, *et al.* Delivery of gold nanoparticles to the brain by conjugation with a peptide that recognizes the transferrin receptor. Biomaterials. 2012;33(29):7194-205.
75. Hsieh S, Chang CW, Chou HH. Gold nanoparticles as amyloid-like fibrillogenesis inhibitors. Colloids and Surfaces B: Biointerfaces. 2013;112:525-9.
76. Yoo J, Lee E, Kim HY, Youn DH, Jung J, Kim H, *et al.* Electromagnetized gold nanoparticles mediate direct lineage reprogramming into induced dopamine neurons *in vivo* for Parkinson's disease therapy. Nature nanotechnology. 2017;12(10):1006-14.
77. Tang J, Xiong L, Zhou G, Wang S, Wang J, Liu L, *et al.* Silver nanoparticles crossing through and distribution in the blood-brain barrier *in vitro*. Journal of nanoscience and nanotechnology. 2010;10(10):6313-7.
78. Alam Bony B, Kievit FM. A role for nanoparticles in treating traumatic brain injury. Pharmaceutics. 2019;11(9):473.
79. Lombardo D, Kiselev MA, Caccamo MT. Smart nanoparticles for drug delivery application: development of versatile nanocarrier platforms in biotechnology and nanomedicine. Journal of nanomaterials. 2019; 2019.
80. Huang CL, Hsiao IL, Lin HC, Wang CF, Huang YJ, Chuang CY. Silver nanoparticles affect on gene expression of inflammatory and neurodegenerative responses in mouse brain neural cells. Environmental research. 2015;136:253-63.
81. Migliore L, Uboldi C, Di Bucchianico S, Coppedè F. Nanomaterials and neurodegeneration. Environmental and molecular mutagenesis. 2015;56(2):149-70.
82. Manshadi MK, Saadat M, Mohammadi M, Shamsi M, Dejam M, Kamali R, *et al.* Delivery of magnetic micro/nanoparticles and magnetic-based drug/cargo into arterial flow for targeted therapy. Drug delivery. 2018;25(1):1963-73.
83. Neuberger T, Schöpf B, Hofmann H, Hofmann M, Von Rechenberg B. Superparamagnetic nanoparticles for biomedical applications: Possibilities and limitations of a new drug delivery system. Journal of Magnetism and Magnetic materials. 2005;293(1):483-96.
84. Hadavi D, Poot AA. Biomaterials for the Treatment of Alzheimer's Disease. Frontiers in bioengineering and biotechnology. 2016;4:49.
85. Ji WH, Xiao ZB, Liu GY, Zhang X. Development and application of nano-flavor-drug carriers in neurodegenerative diseases. Chinese Chemical Letters. 2017;28(9):1829-34.
86. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles-based drug delivery systems. Colloids and surfaces B: biointerfaces. 2010;75(1):1-8.
87. Chiellini F, Piras AM, Errico C, Chiellini E. Micro/nanostructured polymeric systems for biomedical and pharmaceutical applications. Nanomedicine. 2008;3(3):367-93.
88. Shakeri S, Ashrafizadeh M, Zarrabi A, Roghanian R, Afshar EG, Pardakhty A, *et al.* Multifunctional polymeric nanoplatforms for brain diseases diagnosis, therapy and theranostics. Biomedicines. 2020 Jan 13;8(1):13.
89. Cai Q, Wang L, Deng G, Liu J, Chen Q, Chen Z. Systemic delivery to central nervous system by engineered PLGA nanoparticles. American journal of translational research. 2016;8(2):749.
90. Calzoni E, Cesaretti A, Polchi A, Di Michele A, Tancini B, Emiliani C. Biocompatible polymer nanoparticles for drug delivery applications in cancer and neurodegenerative disorder therapies. Journal of functional biomaterials. 2019;10(1):4.
91. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. Journal of controlled release. 2012;161(2):505-22.
92. Kuo YC, Lin PI, Wang CC. Targeting nevirapine delivery across human brain microvascular endothelial cells using transferrin-grafted poly (lactide-co-glycolide) nanoparticles. Nanomedicine. 2011;6(6):1011-26.
93. Kuo YC, Tsai HC. Rosmarinic acid-and curcumin-loaded polyacrylamide-cardiolipin-poly (lactide-co-glycolide) nanoparticles with conjugated 83-14 monoclonal antibody to protect β-amyloid-insulted neurons. Materials Science and Engineering: C. 2018;91:445-57.
94. Chen J, Zhang C, Liu Q, Shao X, Feng C, Shen Y, et al. *Solanum tuberosum* lectin-conjugated PLGA nanoparticles for nose-to-brain delivery: *in vivo* and *in vitro* evaluations. Journal of drug targeting. 2012;20(2):174-84.
95. Malmo J, Sandvig A, Vårum KM, Strand SP. Nanoparticle mediated P-glycoprotein silencing for improved drug delivery across the blood-brain barrier: a siRNA-chitosan approach. PloS one. 2013;8(1):e54182.
96. Cha C, Shin SR, Annabi N, Dokmeci MR, Khademhosseini A. Carbon-based nanomaterials: multifunctional materials for biomedical engineering. ACS nano. 2013;7(4):2891-7.
97. Liu J, Cui L, Losic D. Graphene and graphene oxide as new nanocarriers for drug delivery applications. Acta biomaterialia. 2013;9(12):9243-57.
98. Biju V. Chemical modifications and bioconjugate reactions of nanomaterials for sensing, imaging, drug delivery and therapy. Chemical Society Reviews. 2014;43(3):744-64.
99. Zhou K, Thouas GA, Bernard CC, Nisbet DR, Finkelstein DI, Li D, *et al.* Method to impart electro-and biofunctionality to neural scaffolds using graphene-polyelectrolyte multilayers. ACS applied materials and interfaces. 2012;4(9):4524-31.
100. Zhou K, Motamed S, Thouas GA, Bernard CC, Li D, Parkington HC, *et al.* Graphene functionalized scaffolds reduce the inflammatory response and supports endogenous neuroblast migration when implanted in the adult brain. PloS one. 2016;11(3):e0151589.
101. Mohajeri M, Behnam B, Barreto GE, Sahebkar A. Carbon nanomaterials and amyloid-beta interactions: potentials for the detection and treatment of Alzheimer's disease? Pharmacological research. 2019;143:186-203.
102. Hsieh FY, Zhilenkov AV, Voronov II, Khakina EA, Mischenko DV, Troshin PA, *et al.* Water-soluble fullerene derivatives as brain medicine: surface chemistry determines if they are neuroprotective and antitumor. ACS Applied Materials and Interfaces. 2017;9(13):11482-92.
103. Cellot G, Ballerini L, Prato M, Bianco A. Neurons are able to internalize soluble carbon nanotubes: new opportunities or old risks? Small. 2010;6(23):2630-3.
104. Singh BG, Baburao C, Pispati V, Pathipati H, Muthy N, Prassana SR, *et al.* Carbon nanotubes. A novel drug delivery system. International Journal of Research in Pharmacy and Chemistry. 2012;2(2):523-32.
105. Dizaj SM, Mennati A, Jafari S, Khezri K, Adibkia K. Antimicrobial activity of carbon-based nanoparticles. Advanced pharmaceutical bulletin. 2015;5(1):19.
106. Komane PP, Choonara YE, du Toit LC, Kumar P, Kondiah PP, Modi G, *et al.* Diagnosis and treatment of neurological and ischemic disorders employing carbon nanotube technology. Journal of Nanomaterials. 2016; 2016.
107. Cellot G, Cilia E, Cipollone S, Rancic V, Sucapane A, Giordani S, *et al.* Carbon nanotubes might improve neuronal performance by favouring electrical shortcuts. Nature nanotechnology. 2009;4(2):126-33.
108. Matsumoto K, Sato C, Naka Y, Kitazawa A, Whitby RL, Shimizu N. Neurite outgrowths of neurons with neurotrophin-coated carbon nanotubes. Journal of bioscience and bioengineering. 2007;103(3):216-20.
109. Bokara KK, Kim JY, Lee YI, Yun K, Webster TJ, Lee JE. Biocompatability of carbon nanotubes with stem cells to treat CNS injuries. Anatomy and cell biology. 2013;46(2):85-92.
110. Grothe M, Heinsen H, Teipel S. Longitudinal measures of cholinergic forebrain atrophy in the transition from healthy aging to Alzheimer's disease. Neurobiology of aging. 2013;34(4):1210-20.

111. Danysz W, Parsons CG. Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine-searching for the connections. British journal of pharmacology. 2012;167(2):324-52.
112. Revett TJ, Baker GB, Jhamandas J, Kar S. Glutamate system, amyloid β peptides and tau protein: functional interrelationships and relevance to Alzheimer disease pathology. Journal of Psychiatry and Neuroscience. 2013;38(1):6-23.
113. Ferris SH, Farlow M. Language impairment in Alzheimer's disease and benefits of acetylcholinesterase inhibitors. Clinical interventions in aging. 2013:1007-14.
114. Teleanu DM, Chircov C, Grumezescu AM, Teleanu RI. Neuronanomedicine: An up-to-date overview. Pharmaceutics. 2019;11(3):101.
115. Xie J, Shen Z, Anraku Y, Kataoka K, Chen X. Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. Biomaterials. 2019;224:119491.
116. Obermeyer JM, Tuladhar A, Payne SL, Ho E, Morshead CM, Shoichet MS. Local delivery of brain-derived neurotrophic factor enables behavioral recovery and tissue repair in stroke-injured rats. Tissue Engineering Part A. 2019;25(15-16):1175-87.
117. Chakroun RW, Zhang P, Lin R, Schiapparelli P, Quinones-Hinojosa A, Cui H. Nanotherapeutic systems for local treatment of brain tumors. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2018;10(1):e1479.
118. Patel T, Zhou J, Piepmeier JM, Saltzman WM. Polymeric nanoparticles for drug delivery to the central nervous system. Advanced drug delivery reviews. 2012;64(7):701-5.
119. Neeves KB, Sawyer AJ, Foley CP, Saltzman WM, Olbricht WL. Dilation and degradation of the brain extracellular matrix enhances penetration of infused polymer nanoparticles. Brain research. 2007;1180:121-32.
120. Kells AP, Hadaczek P, Yin D, Bringas J, Varenika V, Forsayeth J, *et al.* Efficient gene therapy-based method for the delivery of therapeutics to primate cortex. Proceedings of the National Academy of Sciences. 2009;106(7):2407-11.
121. Yazdan-Shahmorad A, Diaz-Botia C, Hanson TL, Kharazia V, Ledochowitsch P, Maharbiz MM, *et al.* A large-scale interface for optogenetic stimulation and recording in nonhuman primates. Neuron. 2016;89(5):927-39.
122. Yazdan-Shahmorad A, Tian N, Kharazia V, Samaranch L, Kells A, Bringas J, *et al.* Widespread optogenetic expression in macaque cortex obtained with MR-guided, convection enhanced delivery (CED) of AAV vector to the thalamus. Journal of neuroscience methods. 2018;293:347-58.
123. Masserini M. Nanoparticles for brain drug delivery. International Scholarly Research Notices. 2013; 2013.
124. Silva Adaya D, Aguirre-Cruz L, Guevara J, Ortiz-Islas E. Nanobiomaterials' applications in neurodegenerative diseases. Journal of biomaterials applications. 2017;31(7):953-84.
125. Rahaman ST. A Review on Treatment for Neurodegenerative disease with the help of Nanosciences. World Journal of Pharmaceutical Sciences. 2018:153-62.
126. Johnsen KB, Bak M, Kempen PJ, Melander F, Burkhart A, Thomsen MS, *et al.* Antibody affinity and valency impact brain uptake of transferrin receptor-targeted gold nanoparticles. Theranostics. 2018;8(12):3416.
127. Toccaceli G, Barbagallo G, Peschillo S. Low-intensity focused ultrasound for the treatment of brain diseases: safety and feasibility. Theranostics. 2019;9(2):537.
128. Singh AK, Yadav TP, Pandey B, Gupta V, Singh SP. Engineering nanomaterials for smart drug release: Recent advances and challenges. Applications of targeted nano drugs and delivery systems. 2019:411-49.
129. Jagannathan J, Sanghvi NT, Crum LA, Yen CP, Medel R, Dumont AS, *et al.* High-intensity focused ultrasound surgery of the brain: part 1-a historical perspective with modern applications. Neurosurgery. 2009;64(2):201-11.
130. Jang HJ, Lee JY, Lee DH, Kim WH, Hwang JH. Current and future clinical applications of high-intensity focused ultrasound (HIFU) for pancreatic cancer. Gut and liver. 2010;4(Suppl 1):S57.
131. Curley CT, Sheybani ND, Bullock TN, Price RJ. Focused ultrasound immunotherapy for central nervous system pathologies: challenges and opportunities. Theranostics. 2017;7(15):3608.
132. Jordão JF, Ayala-Grosso CA, Markham K, Huang Y, Chopra R, McLaurin J, *et al.* Antibodies targeted to the brain with image-guided focused ultrasound reduces amyloid-β plaque load in the TgCRND8 mouse model of Alzheimer's disease. PloS one. 2010;5(5):e10549.
133. Raymond SB, Treat LH, Dewey JD, McDannold NJ, Hynynen K, Bacskai BJ. Ultrasound enhanced delivery of molecular imaging and therapeutic agents in Alzheimer's disease mouse models. PloS one. 2008;3(5):e2175.
134. Wang F, Shi Y, Lu L, Liu L, Cai Y, Zheng H, *et al.* Targeted delivery of GDNF through the blood-brain barrier by MRI-guided focused ultrasound. PLoS One. 2012;7(12):e52925.
135. Qin Y, Chen H, Zhang Q, Wang X, Yuan W, Kuai R, *et al.* Liposome formulated with TAT-modified cholesterol for improving brain delivery and therapeutic efficacy on brain glioma in animals. International journal of pharmaceutics. 2011;420(2):304-12.
136. Kuai R, Yuan W, Qin Y, Chen H, Tang J, Yuan M, *et al.* Efficient delivery of payload into tumor cells in a controlled manner by TAT and thiolytic cleavable PEG co-modified liposomes. Molecular pharmaceutics. 2010;7(5):1816-26.
137. Zheng C, Ma C, Bai E, Yang K, Xu R. Transferrin and cell-penetrating peptide dual-functioned liposome for targeted drug delivery to glioma. International journal of clinical and experimental medicine. 2015;8(2):1658.
138. Madani F, Lindberg S, Langel Ü, Futaki S, Gräslund A. Mechanisms of cellular uptake of cell-penetrating peptides. Journal of biophysics. 2011; 2011.
139. Bechara C, Sagan S. Cell-penetrating peptides: 20 years later, where do we stand? FEBS letters. 2013;587(12):1693-702.
140. Eugenin EA, Clements JE, Zink MC, Berman JW. Human immunodeficiency virus infection of human astrocytes disrupts blood-brain barrier integrity by a gap junction-dependent mechanism. Journal of Neuroscience. 2011;31(26):9456-65.
141. Zhu X, Jin K, Huang Y, Pang Z. Brain drug delivery by adsorption-mediated transcytosis. In Brain targeted drug delivery system. 2019:159-83. Academic Press.
142. Nowak M, Helgeson ME, Mitragotri S. Delivery of nanoparticles and macromolecules across the blood-brain barrier. Advanced Therapeutics. 2020;3(1):1900073.
143. Wen X, Wang K, Zhao Z, Zhang Y, Sun T, Zhang F, *et al.* Brain-targeted delivery of trans-activating transcriptor-conjugated magnetic PLGA/lipid nanoparticles. PloS one. 2014;9(9):e106652.
144. Masuda H, Hirata A, Kawai H, Wake K, Watanabe S, Arima T, *et al.* Local exposure of the rat cortex to radiofrequency electromagnetic fields increases local cerebral blood flow along with temperature. Journal of Applied Physiology. 2011;110(1):142-8.
145. Tabatabaei SN, Duchemin S, Girouard H, Martel S. Towards MR-navigable nanorobotic carriers for drug delivery into the brain. In2012 IEEE International Conference on Robotics and Automation 2012:727-32. IEEE.
146. Jones RM, Deng L, Leung K, McMahon D, O'Reilly MA, Hynynen K. Three-dimensional transcranial microbubble imaging for guiding volumetric ultrasound-mediated blood-brain barrier opening. Theranostics. 2018;8(11):2909.
147. Sun Z, Worden M, Wroczynskyj Y, Yathindranath V, van Lierop J, Hegmann T, *et al.* Magnetic field enhanced convective diffusion of iron oxide nanoparticles in an osmotically disrupted cell culture model of the blood-brain barrier. International journal of nanomedicine. 2014:3013-26.
148. Kievit FM, Zhang M. Surface engineering of iron oxide nanoparticles for targeted cancer therapy. Accounts of chemical research. 2011;44(10):853-62.
149. Xu C, Sun S. New forms of superparamagnetic nanoparticles for biomedical applications. Advanced drug delivery reviews. 2013;65(5):732-43.
150. Olaru DG, Olaru A, Kassem GH, Popescu-Driga MV, Pinosanu LR, Dumitrascu DI, *et al.* Toxicity and health impact of nanoparticles. Basic biology and clinical perspective. Rom. J. Morphol. Embryol. 2019;60:787-92.
151. Bencsik A, Lestaevel P, Canu IG. Nano-and neurotoxicology: An emerging discipline. Progress in neurobiology. 2018;160:45-63.
152. Wen MM, El-Salamouni NS, El-Refaie WM, Hazzah HA, Ali MM, Tosi G, *et al.* Nanotechnology-based drug delivery systems for Alzheimer's disease management: Technical, industrial and clinical challenges. Journal of Controlled Release. 2017;245:95-107.

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