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Blood-Brain Delivery Methods Using Nanotechnology

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ABSTRACT

Blood–brain barrier (BBB) is a natural protective membrane that prevents central nervous system (CNS) from toxins and pathogens in blood. However, the presence of BBB complicates the pharmacotherapy for CNS disorders as the most chemical drugs and biopharmaceuticals have been impeded to enter the brain. Insufficient drug delivery into the brain leads to low therapeutic efficacy as well as aggravated side effects due to the accumulation in other organs and tissues. Nanotechnology-enabled drug delivery systems have emerged as a promising tool for overcoming the Blood Brain Barrier (BBB) and delivering drugs to the Central Nervous System (CNS). This mini-review provides an overview of recent advancements in nanotechnology to improve blood-brain barrier penetration. It covers different approaches, such as using targeted ligands and receptors, engineered carriers and transporters, and surface modifications for targeting the blood-brain barrier. Polymeric nanoparticles, liposomes, and metallic nanoparticles, such as silver and zinc oxide, are discussed in the context of their unique properties and applications. Preclinical and clinical advances in nanotechnology-based BBB delivery are discussed, including transcellular nanotechnology-based brain drug delivery and preclinical and clinical studies of nanocarriers for CNS disorders. Although nanotechnology has shown great potential for treating CNS diseases, several challenges remain. The major challenges and future perspectives for constructing brain-targeted delivery systems are also discussed, particularly limitations associated with the blood-brain barrier and clinical obstacles to CNS disease treatment.

Keywords: Nanoparticles; Blood brain barrier; Drug delivery systems; engineered carriers, Alzheimer disease, Liposomes.

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INTRODUCTION

Brain diseases, including brain cancer, Alzheimer's disease, Parkinson's disease, stroke, and multiple sclerosis, are some of the most prevalent diseases, which are becoming a great concern due to the increase in elderly population.[1]

1. These disorders may be caused by genetic and environmental factors, pathologies in processes involving protein aggregation which lead to neuro degeneration or dysregulation of the immune process, or abnormalities regarding the development and function of the brain.[2]
2. However, compared to other areas of an organism, the treatment for brain diseases is presently unsuccessful mostly due to the complexity of the brain. Additionally, drug development for brain diseases requires longer periods of time and more complex clinical trials. Since the number of cases are expected to increase over the following years, the discovery of novel and improved strategies is crucial.
3. The pathways for the delivery of therapeutic agents to the brain can either be invasive or non-invasive. The invasive route involves the surgical administration of drugs directly inside the brain, thus providing a sufficient dosage without causing systemic toxicity. However, the intracerebral injection relies on the cerebral diffusion, thus being concentration-dependent and decreasing from the administration site.[3] The non-invasive administration strategies are based on the anatomical structure of the brain capillaries, cells, and extracellular environment, and on the directional transfer of fluids across the brain, the main routes including the nasal and the systemic administration.
4. The nasal route is preferred over the systemic drug delivery as the drug is directly delivered into the brain through the olfactory bulb, which increases the bioavailability and reduces the degradation of the drug. Nevertheless, limitations such as poor drug permeations through the nasal mucosa and monocular clearance might be encountered.
5. Considering the systemic route, the circulating drugs must enter the parenchyma and the cerebrospinal fluid and further diffuse through the brain extracellular space to the targeted site.
6. The blood-brain barrier is the structure responsible for the protection of the brain, acting as a local gateway against the circulating toxins and cells.
7. Through a selective permeability system. Hence, the delivery systems for the treatment of brain diseases should have the capacity to cross the blood-brain barrier without causing immune responses. However, the physiological function of the blood-brain barrier is the

key challenge for the delivery of pharmaceutical drugs to the brain, which represents the main reason for complications in the existing treatment strategies and for the numerous research studies focusing on the development of novel drug delivery systems for the treatment of brain-associated diseases.

8. The principal pathways for crossing the blood-brain barrier are through paracellular transport, between endothelial cells, and through transcellular transport, involving passive or active mechanisms, across the luminal side of the endothelial cells, through the cytoplasm, and subsequently across the abluminal side, into the brain.
9. Although there are multiple crossing pathways, approximately 98% of small molecules and most large molecules are unable to reach the brain through the blood-brain barrier.[4]
10. Nanotechnology, the emerging field that encompasses knowledge from multiple disciplines including chemistry, physics, engineering, and biology, implicates the development and modification of materials within the size range of 1–100 nm in at least one dimension.

The Blood- Brain Barrier

The central nervous system compartment, consisting of the brain and the spinal cord, is protected by two main barriers: the blood-brain barrier, formed by the brain microvascular endothelial cells, and the blood-cerebrospinal fluid barrier, comprised of the epithelial layer of choroid plexus, the cerebral ventricles, and the arachnoid mater covering the outer brain surface.

As the subject of this review, the blood-brain barrier is characterized by its unique structure and the highly controlled interactions between its cellular and a cellular components. The main function of the blood-brain barrier is to ensure an optimal environment for the proper functionality of the neuronal network, by maintaining brain homeostasis, regulating the influx and efflux of fluids, and protecting the brain against pathogenic agents through a dynamic combination of cellular, vascular, molecular, and ionic factors. Additionally, it contributes to the neuronal. [5]

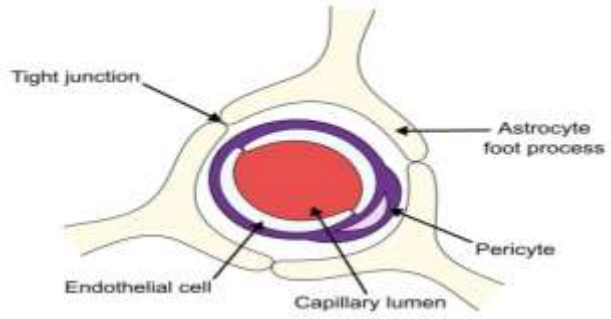


Figure 1: Structure of blood brain barrier.

The main component of the blood-brain barrier is the continuous layer of endothelial cells connected through tight junctions composed of claudin-5, occludin, and other molecules which represents the luminal surface of more than 99% of the capillaries of the brain and spinal cord Additionally, the blood-brain barrier is composed of specialized cells, including the pericytes, the astrocytes, and the adjacent neurons.

Central nervous system (CNS) diseases

Central nervous system (CNS) diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Epilepsy, stroke, and brain cancers, are major cause of disability and death worldwide. [6]

Alzheimer's disease

AD is characterized by a progressive decline in two or more cognitive domains, including memory, language, executive and visuospatial functions, personality, and behavior, resulting in the loss of ability to execute tools and/or basic activities of daily life A hallmark pathology of AD is the progressive accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and the twisted strands of the protein tau (tangles) inside neurons, these changes are eventually accompanied by the loss of synapses and neurons. Both abnormal metabolism of Aβ and hyper phosphorylation of tau protein lead to neurodegeneration, and the reduction of acetylcholine (A neurotransmitter) and oxidative stress in the body may also be related factors in the occurrence of AD. Therefore, the occurrence of AD may be a consequence of the interaction of multiple causes. Aβ plaques around the brain, soluble Aβ and tau protein in cerebrospinal fluid are the main biochemical markers of AD, which have been used for clinical diagnosis Current treatments for AD focus on inhibiting the formation of Aβ plaques/tau tangles and neutralizing their aggregation around neurons. Some clinically approved drugs can only relieve symptoms and delay the progression of AD by providing neurotransmitters Therefore, new AD markers and nan medicines targeting AD markers are urgently needed.[7]

Epilepsy

Epilepsy is a brain disorder characterized by large-scale abnormal synchronous firing of neurons, mainly due to an imbalance between excitatory and inhibitory neurotransmission .At present, the first and second generation of antiepileptic drugs (AEDs) are used in clinical management of the disease, which include voltage-dependent sodium channel blockers, activators for extended opening time of chloride channels, and drugs for increased γ-aminobutyric acid (GABA) synthesis or decreased GABA degradation. These drugs act by inhibiting excitatory currents or enhancing inhibitory currents. However, research data show that about 30 % of epilepsy patients

are resistant to AEDs Based on the drug resistance of epilepsy patients to AEDs, two main hypotheses are proposed to explain. The first hypothesis suggests that resistance develops because AEDs cannot penetrate the BBB and enter the brain. This is due to the overexpression of drug efflux transporters in the BBB of epileptic patients resistant to AEDs, which limit the access of AEDs to the brain. The second hypothesis is that the target receptor sites of AEDs are changed in some way in the brains of epileptic patients, resulting in their decreased sensitivity to drugs .Current evidence supports that these two hypotheses are not mutually exclusive and both play a key role in the study of resistance to AEDs. Therefore, the efficacy of AEDs depends on their ability to cross the BBB and bind to target receptor sites recently, nano-delivery systems have attracted attention for their ability to cross the BBB and improve the effectiveness of AEDs, opening up potential prospects for epilepsy treatment.[8]

Stroke

Stroke is one of the most serious neurological diseases that pose a threat to human health, causing substantial long-term disability and even death worldwide. In terms of its physiological and pathological characteristics, stroke is often caused by cerebral vascular stenosis, occlusion or hemorrhage, which leads to the interruption or obstruction of blood supply to brain tissue, resulting in an insufficient supply of nutrition and O2 in the brain region, causing brain cell death and neurological dysfunction, and eventually causing permanent damage to brain tissue .Stroke can be divided into three types, namely ischemic stroke, hemorrhagic stroke and transient ischemic attack. A majority of the patients (87 %) suffer from ischemic stroke. Ischemic stroke is caused by obstruction of blood flow in the CNS. Hemorrhagic stroke is caused by blood leakage due to rupture of blood vessels. A transient ischemic attack occurs due to the formation of a small embolism of a clot that temporarily blocks blood flow.[9] The lack of effective measures for diagnosing and treatment of ischemic stroke still remain challenging Currently, restoring blood flow through thrombolysis and/or thrombectomy are the only approved treatments for ischemic stroke Nano therapy provides great advantages for the effective treatment of stroke in terms of crossing the BBB, improving drug bioavailability, increasing - drug accumulation, and reducing systemic toxicity. Therefore, the nano-drug delivery system has great application prospects as an effective and safe system for delivering therapeutic agents across BBB.[10]

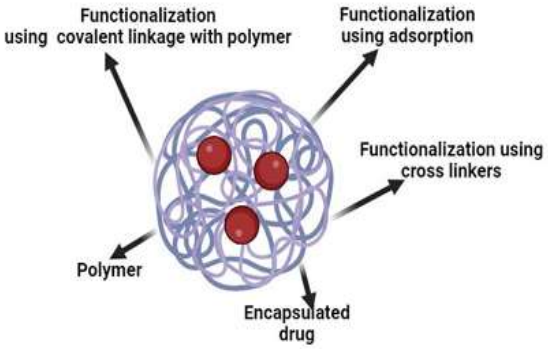
Nanotechnology Approaches for Crossing the Blood-Brain Barrier

Novel insights into the workings of neural circuits and strategies for the diagnosis and treatment of brain disorders will come from the development of nanotechnology through integrated multidisciplinary efforts.

Organic Nanoparticles

Polymeric nanoparticles

The most researched nanoparticle technology for brain delivery is polymeric nanoparticles. They can be made from natural or synthetic polymers. Due to their ability to undergo surface modification (e.g., PEGylation), Nano sizing, bioactivity, controlled and sustained drug release, nontoxicity, bioavailability, biocompatibility, reticuloendothelial clearance bypass, and the encompassing of various active molecules including drugs, oligonucleotides, and peptides, these have developed into one of the most successful candidates for drug delivery applications.[11]



Schematic illustration of a functionalizable polymeric nanoparticle (Ayub & Wettig, 2022)

Figure 2: Over view of polymeric nanoparticles.

Dendrimers

Dendrimers are artificial molecules that resemble trees and have several branching monomers extending from the center core. Generally, dendrimers are employed to transport hydrophobic substances to the targeted brain regions. Because of their easy surface modification, high biocompatibility and biodegradability, superior water solubility, and flexible molecular weight and shape, dendrimers are highly useful for drug administration. Dendrimers also have a passive targeting impact because of their increased permeability and retention [EPR] effect, a property that facilitate BBB penetration.[12]

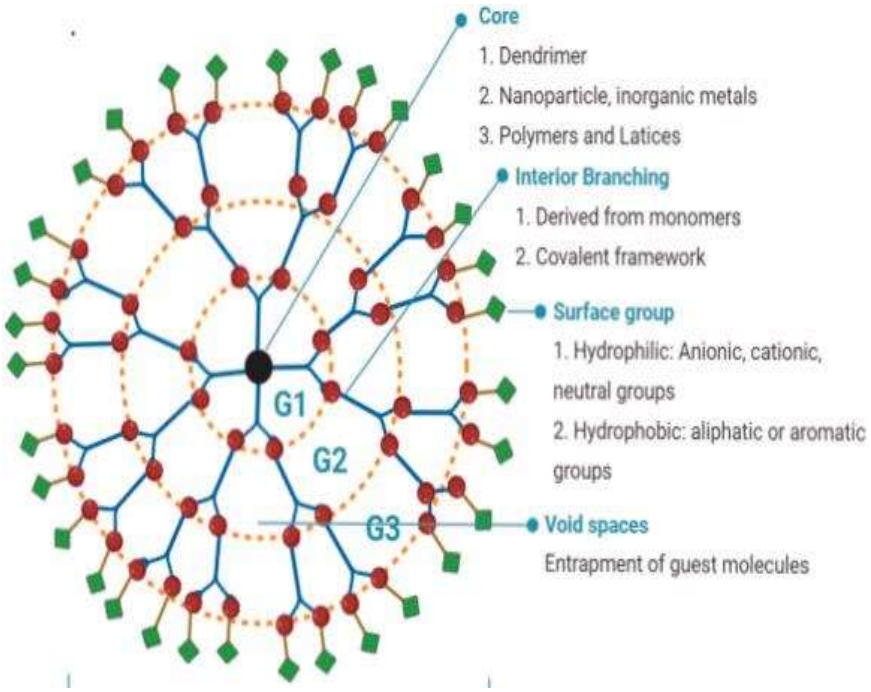


Figure 3: Over view of dendrimers.

Polymeric micelle

In recent years, polymeric micelles have been produced for medication delivery. These micelles exhibit shell core structures with hydrophobic block polymers (such as L, D-lactone polycaprolactone) as the core and hydrophilic block polymers (typically PEGs) as the shell. These micelles develop spontaneously in amphiphilic copolymer solutions.[13] The particle size of the polymeric micelles is reported to be between 10 and 100 nm. It is possible to load water-insoluble medications into the core.

Liposomes

Liposomes are tiny, spherical vesicles made up of one or more phospholipid bilayer concentric spheres divided by aqueous compartments. Because of their hydrophilic core and hydrophobic (lipophilic) tail, they are considered amphiphilic.[14] The majority of their physical characteristics, including size, amphilicity, and surface charge, are modifiable based on the preparation technique and the type and amount of fat employed. Their dimensions might vary from 50 nm to 1 µm. Many liposomal drug-delivery systems have been successfully used for brain drug delivery.

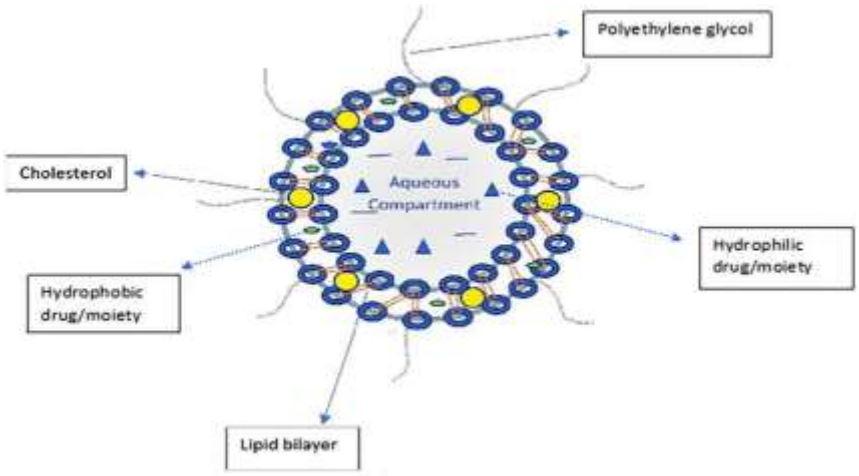


Figure 4: Over view of liposomes.

Inorganic Nanoparticle

Gold nanoparticles

Gold nanoparticles have been commonly studied in the therapy of neurodegenerative diseases through the functionalization with therapeutic macromolecules [15]. The treatment of Alzheimer's disease by using gold nanoparticles functionalized with β-amyloid specific peptides and the treatment of Parkinson's disease with l-DOPA functionalized multi-branched Nano flower-like gold nanoparticles have been studied, showing enhanced blood-brain barrier permeability across in vitro models. [16]

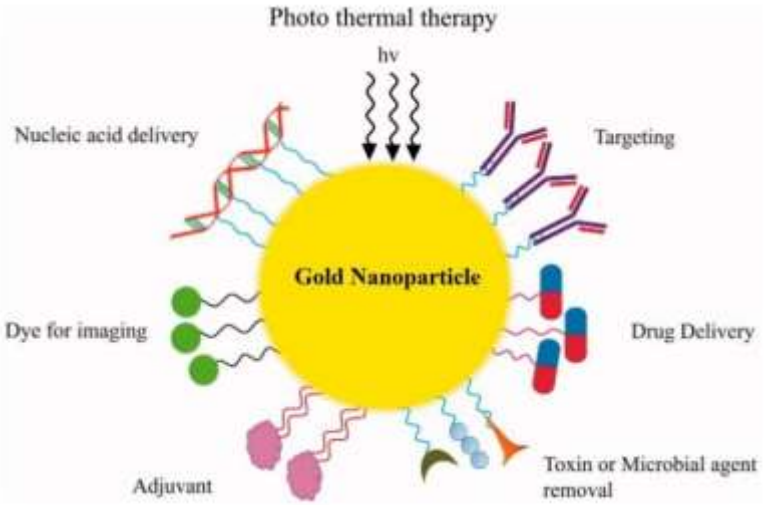


Figure 5: Over view of gold nanoparticles.

CONCLUSION

Nanotechnology-based intranasal drug delivery systems offer a promising a9pproach for enhancing brain targeting and overcoming the limitations of conventional methods. These systems demonstrate improved bioavailability, reduced systemic side effects, and the potential

for precise drug delivery to the central nervous system. While challenges such as enzymatic degradation, limited absorption of certain molecules, and formulation constraints persist, ongoing research continues to address these issues. The development of advanced nanocarriers, coupled with a deeper understanding of nasal physiology and drug transport mechanisms, paves the way for more effective treatments of neurological disorders.

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