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Crossing the blood-brain barrier: Recent Advances in Nano-formulation Strategies for Central Nervous System Drug Delivery in Neurodegeneration and Brain Tumours

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Abstract
Diseases of the central nervous system (CNS) and brain tumours are leading causes of death and disability globally. Drug delivery for CNS illnesses is highly difficult because of the blood-brain barrier (BBB). Medications can be delivered to the central nervous system (CNS) via nano-delivery systems, which can also enhance their ability to target the brain and offer potential therapeutic approaches for CNS disorders. Simultaneously, the therapeutic efficacy of the Nano-drug delivery system can be further optimised by selecting different drug delivery mechanisms (crossing or avoiding the blood-brain barrier). This article reviews the many approaches to Nano-delivery systems that circumvent the BBB to enter the brain. There was a thorough discussion of several nanoparticle types to get around the BBB.

Keywords: Nanoparticles, blood-brain barrier, Nano-drug delivery, neurological diseases, brain tumour

1. INTRODUCTION

There are different types of Central nervous system (CNS) diseases, like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Seizures, stroke, and brain cancer, which are among the major causes of disability and mortality worldwide [1,2]. CNS disorders afflict 17% of the total world population, thus posing grave dangers to human life and an economic burden on societies [3]. 80% of all brain tumours constitute gliomas, being the most common of all. It has been stated that the survival rate after two years for patients with gliomas is improved by just 20-25% through treatments available [4].

The blood-brain barrier (BBB) and blood-tumour barrier (BTB) pose challenges for the administration of therapeutics to the central nervous system because of the strict regulation of the permeation of substances that protect the brain from harm, but at the same time restrict access of drugs into the brain tissue [5]. BBB is a very selective and permeable structure that consists of endothelial cells, pericytes, astrocytes, and basal lamina. The main function of the BBB is the regulation of the transfer of different chemicals from the blood to the CNS according to the physiological needs of the brain. In other words, the BBB prevents the penetration of harmful blood toxins, infections, or any other materials into the CNS. Moreover, the BBB works as a route for waste product elimination from the brain to the bloodstream, as well as nutrient transport to the brain tissues. The BBB guarantees ion homeostasis and regulates neurotransmitter levels,

providing ideal function of the CNS [6]. The main option for chemotherapy is temozolomide (TMZ). Unfortunately, O6-methylguanine methyltransferase (MGMT) expression is increased by demethylation of its promoter region, which leads to widespread tumour resistance. Biodegradable foam sheets (Gliadel implants) can be embedded with controlled release of carmustine following surgical excision, improving survival time by 1.1 to 3.3 months [7].

The utilisation of drug delivery methods through nanoparticles offers promising results in solving problems posed by the blood-brain barrier and improving treatments for brain degenerative diseases. Nanoparticles exhibit unique features, including the ability to package drugs, target certain parts of the brain, and overcome the blood-brain barrier in various ways [8]. Numerous mechanisms, including carrier-mediated transport, receptor-mediated transport, adsorptive-mediated transcytosis, and passive dispersion, allow nanoparticles to pass through the blood-brain barrier.

Through passive diffusion, small, lipophilic compounds can cross the blood-brain barrier even with the help of specific transporters [9]. This review explores the components and features of nanoparticles intended to address the problems posed by the blood-brain barrier in relation to neurodegenerative disorders. This includes the fundamental processes of crossing the blood-brain barrier, the factors that determine the effectiveness of nanoparticles, and many new advancements in nanoparticles for brain diseases [10].

2. THE BLOOD-BRAIN BARRIER

2.1. Brain barriers

Three main barriers that act as protection for the brain include the blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier (BCSFB), and the arachnoid barrier [11, 14]. The choroid plexus epithelium, choroid plexus capillary endothelium, and its basement membrane form a barrier structure called the BCSFB. This acts as a border between the cerebrospinal fluid and blood vessels that may inhibit the passage of certain medications into the cerebrospinal fluid. Because cerebrospinal fluid is renewed three to five times daily, most of the drug is excreted during each session [15, 16].

These properties mean that the BCSFB and the arachnoid membrane are not good candidates for drug delivery. The major site of blood-brain interactions is the BBB, consisting of endothelial cells lining the capillaries. Moreover, the BBB is the major barrier protecting the central nervous system and maintaining brain homeostasis [17]. It demonstrates that the structure and function of the BBB are superior to those of BCSFB and the arachnoid barrier. Consequently, it is crucial to concentrate on the BBB's barrier function in medication distribution.

2.2. Blood-brain barrier

The BBB consists of the cerebral endothelial cells, pericytes, astrocytes, and basement membrane [18]. The tight junctions link these non-fenestrated cells, which have a big impact on molecule passage. One of the main difficulties in disrupting the BBB has been the tight connections [19]. 98% of all drugs that have a small molecular size and even up to 100% of large molecule drugs are not able to cross the intact BBB [5]. The BBB may be disrupted due to brain injury, inflammation, and tumours; therefore, it is called the blood-brain tumour barrier in cancer patients, who are a diverse group of people [20]. Treatment of CNS tumours has been attempted based on these natural mechanisms of breakdown of the BBB. The BBB

disruption in gliomas is not uniform, and many contain regions that remain intact and therefore do not allow access to the CNS by the chemotherapeutic agents [21]. The scattered tumour cells that are beneath the intact BBB are not likely to be targeted by any drug, even if it is able to pass through the enhancing contrast tumour.

Drug compounds are capable of penetrating the BBB in three major ways: enhancing the BBB permeability; bypassing the BBB via direct delivery to the brain; and utilising the natural transport process. It has been suggested that for a compound to penetrate the BBB, it must possess a very small molecular weight (less than 500g/mol), lipophilicity, electrical neutrality, and weak bases [22].

2.3. Blood-tumour barrier

By altering the tumour microenvironment (TME) and harming the blood-brain barrier, CNS tumours create BTB, a leaky barrier. A primary brain tumour is a lump that develops in brain tissue as a result of abnormal growth and proliferation of a particular kind of brain cell [23]. There are several structural abnormalities and poor functionality of the blood-brain barrier (BBB) that are associated with brain tumours (Figure1).

Besides, occludin, fibronectin, laminin, and heparan sulfate are some of the components of the BBB that are degraded by matrix metalloproteinases (MMPs). There is an effect of the number of pericytes on the levels of claudin and occludin at the BBB [24]. Hypoxia-inducible factor-1 (HIF-1) is increased in high-grade gliomas due to rapid tumour growth. As there is an increased demand for oxygen and nutrients, HIF-1 helps in angiogenesis, formation of abnormal vessels, and production of VEGF [25].

Consequently, the BBB is disrupted. The BBB's structural and functional alterations in the presence of tumours differ depending on the part of the brain. As a result, the BBB's permeability varies. The kind, volume, stage, and location of the tumour determine how many of these changes occur [26].

3. PROPERTIES OF BBB THAT ARE ADVANTAGEOUS FOR NANO-DELIVERY SYSTEMS

3.1. Properties of BBB

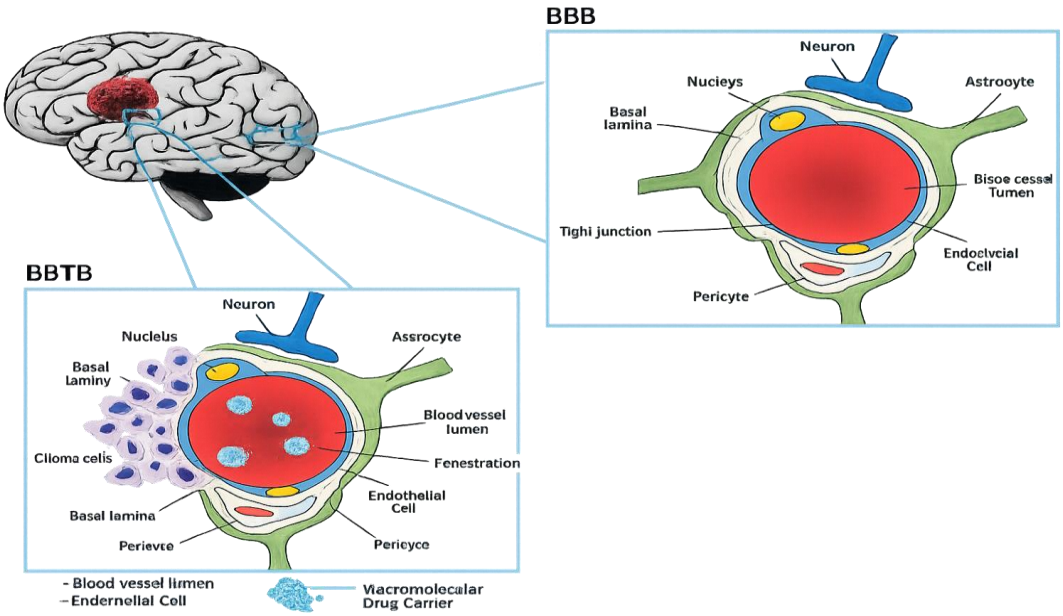

Figure 1. The blood-brain barrier (BBB) and the brain-tumour barrier (BTB)

The selectivity of the BBB is crucial for maintaining brain homeostasis; however, it is an important barrier to the administration of drugs to the tumour site. The formation of tight junctions between endothelial cells significantly hinders passive diffusion through the extracellular matrix. Lipophilic drugs are thus preferred since most of the transport has to be transcellular.

However, as the lipophilicity of drugs increases, they become exposed to many active efflux systems. Doxorubicin, which is a lipophilic drug, is poorly permeable through the BBB due to the active efflux system of the BBB membrane [27]. Degradation of the drugs is yet another problem faced by drugs in penetrating the BBB. Mitochondria-rich cerebral cells contain a membrane of the cerebral endothelium that comes into contact with enzymes that destroy insulin, neprilysin, and encephalin [28].

3.2. Transport mechanism of the brain

Many studies are currently underway to explore multiple pathways that can be used to administer drugs selectively into the brain because of increased knowledge about the BBB and BTB and the changes they undergo due to tumour development (Figure 2) [29].

Due to the presence of tight junctions of the endothelial cells and the intactness of the blood-brain barrier, paracellular transportation cannot take place frequently [27]. It mostly takes place with damaged blood-brain barriers in a minimal manner through the pores of BMECs [30]. In addition, passive diffusion takes place rarely because it is applicable to lipophilic drugs that are less than 500 Daltons [31].

In the case of facilitated diffusion, the direction of movement is along the concentration gradient, while in the case of active transport, the movement is against the concentration gradient. GLUT1, EAAT1, MCT1, and LAT1 are some of the many transporters in the brain [32]. These are responsible for transporting nutrients such as glucose and amino acids. In both the entry of drugs into the brain and their subsequent release from the brain back to the blood, carrier-mediated transport mechanisms play an important role. Hence, active efflux mechanisms might be used to get rid of the drugs transported through this method [33].

Clathrin-mediated endocytosis absorbs these large molecules, which are otherwise called ligands, or caveolin-mediated endocytosis. These methods utilise the formation of vesicles and endosomes that carry the ligands to the brain through the BMECs and release the contents on the abluminal side of the brain. Some of the ligands that are transported this way include LRP1, LRP2, and LDLR. Amphiphysin, endophilin, and various adaptins, dynamins, and rab proteins are among the proteins used as routers for these vesicles [34].

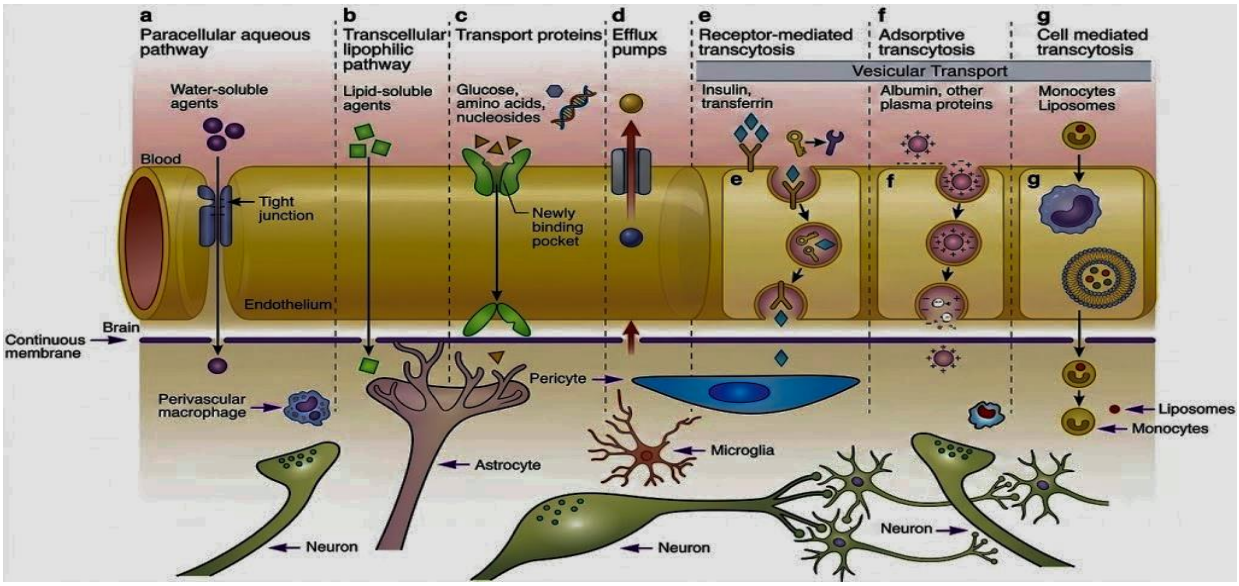

Figure 2. Examples of blood-brain barrier (BBB) transport systems

4. THE CENTRAL NERVOUS SYSTEM (CNS) AND NANOCARRIER-ASSOCIATED DISEASES

4.1. Chronic neurodegenerative diseases

4.1.1. Parkinson's disease

The progressive loss of voluntary motor control is the hallmark of Parkinson's disease (PD), an extremely dangerous age-related neurodegenerative illness. This condition worsens with age and frequently coexists with illnesses like depression, cognitive decline, and sleep disturbances [35–37]. Unfortunately, Parkinson's disease has no recognised cure. Non-specific delivery of levodopa, which is typically used to treat Parkinson's disease (PD), can also have an impact on the peripheral system and cause several adverse effects, including motor symptoms and cardiovascular side effects. [38].

Therefore, an alternative approach to the treatment of Parkinson's disease (PD) is using the nano-carrier system that can cross the BBB and deliver the drugs into the brain.

4.1.2. Alzheimer's disease

The hallmark features of AD include progressive decline in one or more cognitive functions such as memory, language, executive function, visuospatial skills, personality, and behaviour, resulting in the inability to use tools and/or perform basic daily activities [39]. The increased deposition of beta-amyloid protein fragments (plaques) outside neurons and formation of tangled strands of protein tau (tangles) within neurons are two pathological features of AD, which are ultimately associated with synaptic and neuronal loss [40, 41]. Present approaches used in AD treatment are mostly involved in inhibition of the production of Aβ plaques and tau tangles, as well as neutralisation of their accumulation in the proximity of neurons. At the same time, some clinically accepted medications are effective only in symptom relief and slow down the development of AD through neurotransmitter modification [42]. This means that the search for new AD markers and nanomedicines for them is urgently needed.

4.2. Acute neuroinvasive diseases

4.2.1. Epilepsy

Another characteristic feature associated with the occurrence of seizures is massive abnormal neuronal synchronisation, which is caused by disturbances in excitatory and inhibitory neurotransmission in the brain [43]. At present, voltage-gated sodium channel inhibitors, activators that increase chloride channel activation period, and drugs that increase GABA synthesis or reduce GABA catabolism are some examples of first-generation and second-generation AEDs [44].

Two main theories are formulated to account for the development of AED resistance among epileptic patients. The first theory postulates that AED resistance occurs due to the inability of AEDs to penetrate the blood-brain barrier [45, 46]. This happens because people suffering from epilepsy who exhibit AED resistance possess overexpression of drug efflux transporters in their blood-brain barrier, thus preventing AEDs from penetrating the brain. The other theory assumes that people suffering from epilepsy possess different locations of AED receptors in their brains [47].

Based on the information available, these two theories do not contradict each other, and both are essential for the understanding of AED resistance. As a result, the permeability of AEDs through the blood-brain barrier and binding with the receptors play an important role [47]. The recent focus on Nano-delivery systems and the possibility of enhancing the efficiency of AEDs by their ability to pass through the blood-brain barrier is noteworthy.

4.2.2. Stroke

Among many brain disorders that are very harmful to the human body, one of the most perilous brain diseases that may cause disability and even death to humans all around the world is stroke. According to the physiological and pathological characteristics of this disorder, stroke is usually caused by cerebral vascular stenosis, occlusion, or haemorrhage. It leads to the deprivation of blood flow to the brain tissue, causing a deficiency of nutrients and oxygen to the part of the brain, consequently damaging brain cells [48, 49].

The development of neuroprotective drugs used in ischemic strokes at various stages of development and reperfusion is a central area of preclinical investigations. However, most such drugs have poor solubility, limited half-life, which reduces the efficacy of the therapy, and low bioavailability due to the BBB [50, 51].

The use of nanotechnology in addressing the problem of crossing the blood-brain barrier, improving drug bioavailability, increasing drug accumulation, and reducing systemic toxicity can be quite promising for effective therapy of stroke patients. Hence, a nano-drug delivery system provides good prospects for being applied as a safe and effective means for drug delivery.

4.3. Brain tumour

Brain cancers can be categorised as primary brain cancers, where the tumour starts to develop in the brain tissues, and secondary brain cancers, where the spread of cancer cells to brain tissues is due to metastasis. The different types of primary brain cancers are glioblastoma (GBM), astrocytoma, oligodendrocyte glioma, and ependymoma; collectively, they account for around 80% of brain cancers [52, 53].

The safest surgery, followed by radiation in grades and chemotherapy with oral administration of temozolomide and/or insertion of carmustine wafers, is the clinical standard treatment for brain tumours [54, 55]. Nevertheless, there are many disadvantages of surgical resection [56]. For this reason, it becomes critical to overcome the BBB's effect on the brain to treat brain tumours effectively.

5. RECENT NANOFORMULATION STRATEGIES

5.1. Liposomes

Liposomes are small, round vesicles with hydrogels in their centre and containing lipids with a very small amount of water at their core, which can be made either artificially or naturally. The composition of lipids determines the stability, rigidity, and phase transition temperature [57].

Recent advances: Liposomes are being coated with targeting agents, such as monoclonal antibodies or peptides, to enhance tumour targeting while reducing side effects on normal cells [58]. The use of liposomes has been effective because of their ability to deliver medications and genes concurrently by serving as carriers in both chemotherapy and gene therapy [59].

5.2. Nanoparticles

Nanoparticles can be described as sub-microscopic particles, whose sizes usually fall between 1 nm and 100 nm [60]. NPs are being increasingly used in pharmaceutical applications, including drug delivery and bioimaging, owing to their unique physicochemical properties, which include optical properties, among others [61].

The choice of nanomaterials is one of the most significant considerations. Nanoparticles can be prepared from organic compounds (e.g., trehalose, chitosan, PLGA, and PLA, among others) and inorganic compounds (e.g., gold, iron, cerium, molybdenum, silver, zinc oxide, silica, magnetic materials) [61, 62]. NPs should be used sparingly when treating CNS disorders since they have the potential to cause cytotoxicity, immunotoxicity, and neurotoxicity [63].

Several organic nanoparticles exhibit low loading capacity when used for drug delivery, thus limiting their efficiency in several drug delivery applications despite having some medicinal properties relative to inorganic nanoparticles. In order to achieve the best results, one has to consider these factors when comparing organic and inorganic nanoparticles.

5.3. Nanomicelles

Amphiphilic compounds form the basic units of hydrophilic (polar) and hydrophobic (nonpolar) molecules that constitute nanomicelles [64]. Nanomicelles can be used for the transport and encapsulation of hydrophilic drugs and proteins. Some of the unique properties of nanomicelles include structural stability, solubilization of hydrophobic drugs, physicochemical properties (amphiphilic copolymers), pH sensitivity, mucoadhesive properties, specific binding, and sensitivity. Therefore, due to such properties, nanomicelle-based drug delivery systems have some advantages over traditional drug delivery systems, which include biodegradability, targeted delivery, low toxicity, minimal side effects, high solubility of drugs, and intravenous delivery of drugs [65].

5.4. Exosomes

Exosomes are bilayer vesicles that have a diameter of 30 to 150 nm. Various types of cells, such as fibroblasts, immune system cells like T, B, and dendritic cells, adipocytes, and cancerous cells, can secrete them. Moreover, they were isolated from all body fluids, whether healthy or diseased, including blood, urine, breast milk, amniotic fluid, bronchoalveolar lavage fluid, and so on. [66, 67].

For instance, Wu et al. [68] created CSI by loading the sonosensitizer indocyanine green (ICG) after encasing catalase (CAT) in silica nanoparticles (CAT@SiO2). Inspired by macrophages' potential to traverse the blood-brain barrier, CSI was then coated with AS1411 aptamer-modified macrophage EXO to create CSI@Ex-A, which has a long circulation time, good biocompatibility, and effective BBB penetration. According to Zhang et al. [69], EXO-coated DOX-loaded nanoparticles have a high capacity to cross the blood-brain barrier, cause tumour cell apoptosis and ICD, and improve the lifespan of mice with GBM. This suggests that EXO is very capable of transporting medications across the blood-brain barrier.

For example, the existing EXO separation method results in only a small amount of EXO, which increases the cost involved in using it in clinical trials and mass production after approval for therapy [70]. Thus, despite the unique advantages of EXO compared to other nanoparticles, a lot remains to be done before they can be used clinically.

6. CHALLENGES AND FUTURE PERSPECTIVES

Dealing with the issues regarding safety is equally crucial for bringing this area of research into the realm of treatment possibilities. The key thing to remember is that, while delivering the drug into the brain, even the best formulas will inevitably accumulate within other physiological systems, like the kidneys, liver, and spleen, before finally being flushed out of the body [71].

a) Toxicity and Biocompatibility: Long-term toxicity tests are necessary to characterise the toxicity profile of nanocarriers in clinical use, although most of them are designed to be biocompatible [72].
b) Regulatory Issues: Due to the specific features of nanomaterials, regulatory approval for nanomedicines remains difficult to obtain. In order to tackle the peculiar risks associated with innovative technologies, regulatory systems need to evolve [73].
c) Production and Scalability: The large-scale production of nanocarriers is challenging and expensive. In order to decrease the cost and improve scalability, innovations in the field of manufacturing processes are needed [74].
d) Cost: Owing to their complex nature, nanomedicines are often more expensive than conventional drugs. Popularisation of nanomedicines hinges on attempts to reduce the cost of production [75].

CONCLUSION

Numerous disorders, including Alzheimer’s disease (AD), Parkinson’s disease (PD), Multiple Sclerosis (MS), epilepsy, stroke, and brain cancer, can be caused by CNS abnormalities. These illnesses have had a major negative impact on people's health and placed a significant strain on society. Even though technology has advanced significantly, modern treatments for CNS disorders can only provide temporary relief rather than a cure. The BBB is the primary cause of this problem. Therefore, the key to treating CNS illnesses is to overcome the BBB. The pharmacological effects in clinical practice can be influenced by

the shape, size, hydrophobicity, coating, chemical, and surface charge features of nanoparticles, even though many of them can successfully cross the blood-brain barrier. Recent developments in drug release techniques, targeting mechanisms, and Nanocarrier design have created new avenues for treating complicated illnesses like cancer, neurological problems, and infectious diseases.

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