Nano Research
2024, 17(7): 6305–6322

ISSN 1998-0124 CN 11-5974/O4
https://doi.org/10.1007/s12274-024-6598-1

Review Article

Nanoparticle delivery for central nervous system diseases and its clinical application

Lin Tang, Rui Zhang, Yusi Wang, Mohan Liu, Die Hu, Yuanda Wang, and Li Yang (✉)

Department of Biotherapy, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

Received: 28 December 2023 / **Revised:** 27 February 2024 / **Accepted:** 28 February 2024

ABSTRACT

In the treatment of central nervous system (CNS) diseases such as glioma, Alzheimer's disease (AD) and Parkinson's disease (PD), drugs are expected to reach specific areas of the brain to achieve the desired effect. Although a growing number of therapeutic targets have been identified in preclinical studies, the ones that can ultimately be used in the clinic are limited. Therefore, the research process and clinical application of drugs for treating CNS diseases are still large challenges. Physiological barriers such as the blood–brain barrier (BBB) act as selective permeable membranes, allowing only certain molecules to enter the brain; this barrier is the major obstacle restricting the arrival of most drugs to brain lesions. Recently, nanoparticles, including lipid-based, cell-derived biomimetic, polymeric and inorganic nanoparticles, have gained increasing attention because of their ability to cross physiological barriers, and could play an important role as delivery carriers and immunomodulators. Additionally, clinical applications of nanoparticles in CNS diseases are underway. This review focuses on the progress of current research on the use of nanoparticles for the treatment of CNS diseases to provide additional insight into the treatment of CNS diseases.

KEYWORDS

nanoparticles, central nervous system (CNS) diseases, clinical applications, delivery carriers, immunomodulators

1 Introduction

Central nervous system (CNS) disease, which includes Alzheimer's disease (AD), Parkinson's disease (PD) and brain tumors, is an increasingly serious, difficult and expensive global health problem. Among these conditions, AD and PD are increasingly harmful to the growing elderly population [1], and brain tumors such as gliomas or brain metastases are mainly treated by traditional surgery combined with radiotherapy and chemotherapy; however, the survival time is still less than 15 months [2], which greatly affects patient quality of life. Of course, there is much preclinical research on these diseases, which are becoming increasingly prevalent and showing earlier onset. At present, an increasing number of preclinical studies have explored the pathogenesis of various central nervous system diseases, and new therapeutic targets are gradually being discovered [3]. Although there have been major advances in drugs for treating CNS diseases, many drugs still cannot be effectively used in clinical practice. The main problems with these drugs include the following: (1) They may be inactivated by systemic delivery [4, 5]; (2) they may degrade rapidly in the circulatory system [6] and thus are unable to function; (3) they cause serious systemic side effects [7]; and (4) they are restricted by physiological barriers, including the blood-brain barrier (BBB), which restricts the entry of almost all macromolecular drugs and 98% of small molecule drugs [8]. Therefore, the development of carriers that can carry therapeutic drugs across physiological barriers to brain lesions is key for the treatment of CNS diseases.

Nanoparticles are a class of materials based on the design, synthesis and characterization of various molecules and technologies, and their minimum functional size is at the nanoscale [9]. Nanoparticles designed based on nanotechnology are conducive to changing the size, shape, or charge of drugs and materials, thereby facilitating the control of various properties [10], thus making themselves advantageous for the treatment of CNS diseases. In addition, nanoparticles can be used as carriers for therapeutic drugs, enhance drug permeability and cross physiological barriers to reach brain lesions. Currently, the most commonly used types of nanoparticles are lipid-based, polymeric and inorganic [11, 12], and novel nanoparticles, such as combination of exosomes and modified extracellular vesicles (EVs) [13], have also being explored. Currently, an increasing number of clinical applications for treating CNS diseases focused on the use of nanomaterials. Thus, in this review, we summarize the progress and clinical application of nanoparticles in CNS diseases to provide an overview of the development of such drugs for the treatment of CNS diseases.

2 Central nervous system diseases

2.1 Several major CNS diseases

CNS diseases include brain tumors, stroke, traumatic brain injury, and neurodegenerative diseases such as AD and PD, which have serious impacts on human health. Here, we introduce several major CNS diseases (Fig. 1).

Address correspondence to yl.tracy73@gmail.com

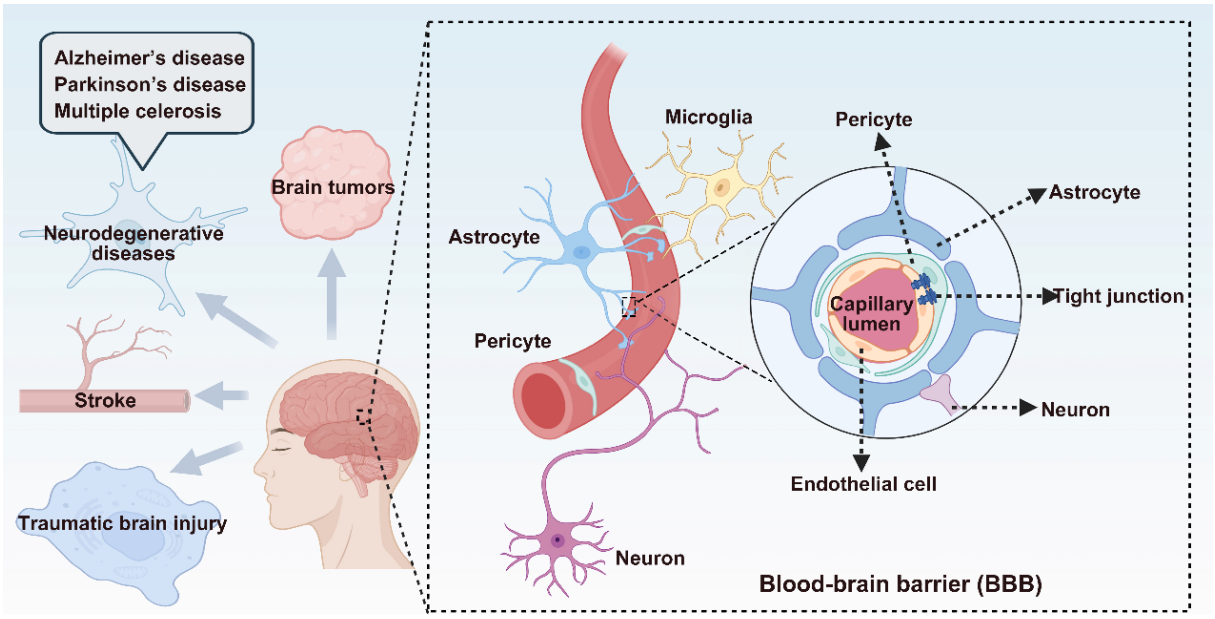

Figure 1 Major CNS diseases and the structure of BBB. Major CNS diseases include brain tumors, neurodegenerative diseases, stroke and traumatic brain injury. The BBB is shaped by endothelial cells, pericytes, and astrocytes, and the formation of tight junctions restricts the passage of most drugs. Microglia and neurons surround blood vessels.

2.1.1 *Brain tumors*

Although brain tumors account for only 2% of newly diagnosed cancers, they are still a major cause of cancer death [14]. In addition to the adverse reactions caused by the primary brain tumor and metastasize tumors, patients with brain tumors often suffer serious complications because of the damages caused by tumor in important areas of brain. Most brain tumors, especially malignant gliomas, have high recurrence rate and still remain malignant even after intensive primary treatment [14]. Glioma is the primary type of brain tumor, accounting for 80% of malignant brain tumors, and can occur anywhere in the CNS [15]. Despite numerous efforts, including surgery, radiotherapy, and chemotherapy, the overall median survival (OS) of patients after diagnosis is still less than 15 months, which represents a major challenge in glioma treatment [2].

At present, cancer immunotherapy is widely used to treat a variety of cancers. Brain tumors, especially gliomas, are heterogeneous for different patients. Recognition of immune-associated antigens is a key factor in treatment for each patient [16]. Since it is difficult for identifying just one single target, for most patients, combination of multiple antigens is crucial for good clinical effect. Studies of combined antigen-specific chimeric antigen receptor T cell (CAR-T) have been proposed to prevent antigen immune escape, and these therapies are expected to enter clinical trials [17, 18]. In addition, immune checkpoint blockade alone or therapies in combination with engineered T-cell may also be effective for overcoming tumor heterogeneity because multiple patient-specific mutations can be targeted simultaneously, which would enhance the breadth of antitumor immune responses [14].

Vascular dysfunction, including vascular irregularity and increased permeability, may be present in the vessels of patients with gliomas but not in healthy cerebrovascular vessels. Changes in the vasculature can also affect brain tumor tissue [1]. In addition, glioma cells secrete cytokines that recruit immune cells, including tumor-associated macrophages, bone marrow-derived suppressor cells and T cells, into brain tumors, thereby remodeling the tumor microenvironment [1, 19].

2.1.2 *Neurodegenerative diseases*

Neurodegenerative diseases, including mainly AD and PD, are caused by the degeneration of neurons or their myelin sheaths, which deteriorate over time and become dysfunctional.

AD is a neurodegenerative brain disease in which damage to brain cells worsens over time and is characterized by two main types of neuropathological lesions: extracellularly accumulated β-amyloid plaques and increased intracellular microtubule-associated tau protein, which leads to the formation of neurofibrillary tangles [20]. In addition, increasing evidence indicates that cerebrovascular dysfunction is an early pathological event in AD and plays an important role in the permanent loss of neuronal function [21]. At present, related studies are underway for the identified pathogenic factors.

PD is the second most common neurodegenerative disorder after AD. It affects approximately 2%–3% of the population aged more than 65 worldwide [22], and is characterized by the loss of dopaminergic neurons in the substantia nigra dense region of the brain and the formation of intracytoplasmic Lewy bodies due to the accumulation of misfolded α-synuclein [23]. α-synuclein is a natural unfolded protein with high concentration in dopaminergic neurons and is considered as a key component of PD-related intracellular deposition [24]. Its toxicity has been proven to damage cell membranes, increase oxidative stress, depolarize mitochondria, and interfere with protein clearance pathways and changes [25, 26]. Therefore, corresponding drugs are being developed.

Multiple sclerosis, a chronic, inflammatory, demyelinating and neurodegenerative disease of the CNS, is caused by complex gene–environment interactions [27]. Multiple sclerosis is also one of the most widely studied epidemiological neurological diseases and is the leading cause of nontraumatic disability in young and middle-aged adults. The pathology of multiple sclerosis is characterized by the accumulation of demyelinating lesions in the white and gray matter areas of the brain and spinal cord, and destruction of the BBB. However, currently, the specific mechanism of BBB breakdown is poorly understood.

2.1.3 *Stroke*

Stroke is the second leading cause of death worldwide and causes long-term disability for tens of millions of people, placing an enormous burden on patients and society. Stroke patients are

mainly divided into ischemic stroke and hemorrhagic stroke groups. Ischemic stroke is a vascular disease of the CNS caused by thrombosis of the cerebral artery. Due to reduced blood flow to the brain, ischemia and hypoxia lead to abnormal brain tissue metabolism, which in turn leads to neuronal damage and neuroinflammation [28]. Additionally, the incidence of hemorrhagic stroke, including subarachnoid hemorrhage and cerebral hemorrhage, has been high in recent decades [29]. The pathogenesis of hemorrhagic stroke involves a variety of molecular and cellular events, such as inflammation, apoptosis, and oxidative stress [30–32]. These cellular events may eventually lead to cell death and brain damage. Therefore, it is important to study the pathophysiological mechanism of hemorrhagic stroke and develop effective treatment drugs. Due to the complexity of the mechanism of cerebral injury caused by cerebral hemorrhage or ischemic stroke, multitarget drugs and multimodal combination therapy may be important directions for improving the prognosis of stroke patients. Currently, intravenous administration is the most commonly used route of administration, while other routes of administration, such as intranasal or local administration, may result in higher concentrations in target tissues and minimize the risk of systemic toxicity [33].

2.1.4 Traumatic brain injury

Traumatic brain injury (TBI) affects people of all ages and is a leading cause of death and disability. Craniocerebral injury mainly includes penetrating injury, that is, the skull and dura are penetrated by objects, directly damage the brain parenchyma, and closed craniocerebral injury occurs where the skull and dura remain intact [34]. According to clinical standards, TBIs are classified as mild, moderate or severe [35]. Mild TBI, also known as concussion, is usually caused by blunt nonpenetrating head trauma. The identification of pathogenic factors involved in TBI at the molecular level showed that TBI involves neuronal cell death, injury to astrocytes and microglial responses, dendritic damage and synaptic dysfunction [35, 36]. The main pathogenic mechanism of trauma is the stretching and tearing of axons, leading to diffuse axonal injury [35]. Although mild brain injury is the most common disorder, the prevalence of disability or memory impairment associated with TBI increases with the severity of TBI, and there is an association between TBI and the risk of dementia. However, the type of dementia associated with TBI is unknown [37, 38].

Currently, there are significant limitations in the treatment of CNS diseases, and the failure of potentially effective therapies in clinical trials is often not due to insufficient drug potency but rather due to the difficulty of delivering drugs effectively to and maintaining drug concentrations in the brain [39]. In response to the shortcomings of conventional delivery mechanisms, researchers are developing and adopting new strategies to deliver active compounds to the CNS more efficiently, with nanoparticle delivery systems as an emerging technology potential to treat the CNS diseases.

2.2 The main factors that limit the effectiveness of drugs

2.2.1 Blood–brain barrier

The BBB is a barrier formed by tightly connected endothelial cells (ECs) and is the core of the brain's neurovascular unit (NVU) [40, 41]. The BBB is considered as one of the most regulated and exclusive barriers in the body. Therefore, it is the major barrier for drug delivery into the brain. Its integrity is maintained by ECs and pericytes [42–45] and is also influenced by astrocytes, especially astrocytes surrounding blood vessels [46] (Fig. 1). ECs are a fundamental component of the BBB and are held together by tight junctions, adherent junctions, and gap junctions. Among them, tight junctions are formed by a variety of transmembrane and cytoplasmic proteins, which are mainly involved in regulating EC permeability, leukocyte migration and cell polarity. Adhesion junctions are formed by transmembrane glycoproteins and are involved in the formation of tight junctions and maintenance of the BBB at the same time. Gap junctions exist between tight junctions and adhesion junctions, allowing the transfer of ions and small molecules between ECs. These junctions are also involved in the regulation of BBB permeability [47–49] and endow ECs with high electrical resistance, such as transendothelial electrical resistance (TEER), which is 100–150 $\Omega \cdot cm^2$ and limits drug transport across the barrier [50]. Pericytes enclose ECs, determine BBB permeability and have many functions, such as strengthening tight junctions and polarizing astrocyte endfeet. In addition, pericytes play a key role in the development and maintenance of the BBB [51]. The endfeet of astrocytes completely cover brain cells and contain several proteins that are essential for proper functioning of the BBB. Additionally, they are important components that link ECs to microglia and neurons [51].

The BBB strictly controls the movement of molecules into and out of the CNS, such as oxygen, carbon dioxide, and small molecular lipophilic molecules that can be transported through the brain endothelium by passive diffusion [52]. However, there are several transport pathways that allow for the delivery of various molecules that play important roles in maintaining brain homeostasis. These include diffuse transport (paracellular and transcellular endocytosis), transporter-mediated endocytosis, receptor-mediated endocytosis, adsorption-mediated endocytosis, and cell-mediated endocytosis pathways [48, 53]. Among them, receptor-mediated endocytosis is a common and effective method for the delivery of therapeutic drugs to the brain and relies on receptors present on the cell surface, mainly transferrin, lactoferrin, insulin, diphtheria toxin, and low-density lipoprotein (LDL) receptors. In addition, this transport pathway is dependent on endocytosis, in which drugs bind to receptors and form intracellular vesicles by membrane invagination [48, 54, 55]. High expression of BBB receptors and targets can increase the efficiency of drug transport across the BBB. Receptor-mediated transcytosis is the most widely used mode of nanoparticle delivery.

2.2.2 Microenvironmental barriers

Once nanoparticles reach the targeted region, they encounter microenvironmental obstacles, including changes in chemical conditions or physical barriers to penetration [56]. Different microenvironments have different characteristics and thus greatly influence the physical properties and stability of nanoparticles. For example, the tumor microenvironment plays an important role in determining whether nanoparticles can function. In general, a low pH in tumors can affect the release of drugs in nanoparticles into tumors. Therefore, pH-sensitive nanoparticles are being developed. Moreover, the tumor microenvironment is heterogeneous, which can affect the permeability of nanoparticles. In the tumor environment, cells may overproduce or produce altered extracellular matrix (ECM) components, resulting in a high density of ECM, thus forming a physical barrier that prevents nanoparticles from entering the lesion [57].

2.2.3 Cellular and intracellular barriers

When drugs enter the brain and contact target cells, they are still restricted by numerous barriers that impede drug uptake and intracellular transport [58]. First, drugs need to be absorbed and internalized by target cells after contact with them to function. The hydrophilicity and electric charge of drugs play important roles in altering cell uptake for many types of cells, including macrophages

and cancer cells [59, 60]. The cell surface consists of a negatively charged, selectively permeable phospholipid bilayer. Therefore, anionic drugs may have difficulty in contacting the cell surface due to the repulsion. Although cationic drugs can be adsorbed by targeted cells through electrostatic adsorption, drugs with excessive positive charges may damage the cell membrane and even cause cytotoxicity [58, 60]. Thus, the first contact between drugs and the targeted cell may determine the fate of drugs.

The next hurdle is the efficiency of drugs taken up by targeted cells, which is largely determined by the shape and size of the drug [61]. Several studies have shown that, in nonphagocytic cells, spherical drugs are more effective than rod-shaped drugs in promoting cell absorption with optimal sizes of 10–60 nanometers, and drugs with smaller size are able to be internalized more effectively [54, 62]. However, other studies have also shown that smaller drugs may cause greater cytotoxicity [63]. The process of drug absorption in target cells can be divided into passive diffusion and active absorption. Passive diffusion mainly depends on the concentration gradient of drugs needed to facilitate diffusion across the membrane into the targeted cell. Indeed, the most common mode of drug transport is active endocytosis, and the mode of drug endocytosis is determined by many factors, including cell type, drug size, and interactions with receptors [58, 64]. In addition, other more specific interactions include endocytosis mediated by either caveolin or clathrin [65]. Therefore, the process of drug ingestion is determined by varies of factors, which need to be considered during drug design.

2.2.4 *The side effects of drugs on other organs*

In general, therapeutic drugs are used to treat specific diseases with the goal of achieving the desired pharmacological effect with minimal side effects. Unfortunately, side effects can occur in a variety of situations, for example, increased frequency or dosage, which was often used to achieve higher efficacy but can cause side effects such as nausea [66]. Additionally, drugs need to target lesions effectively, off-target effects occurred after administration will act on normal organs, which causes a certain degree of damage to those organs. Therefore, the development of nanoparticles that can continuously release drugs may solve this problem by reducing the dose and frequency of administration. Moreover, nanoparticles need to be properly designed and optimized, including different components, surface modifications, component ratios, and charges, to reduce side effects.

3 Nanoparticles

Nanoparticles are defined by the Food and Drug Administration (FDA) as having a particle size of 1–100 nm; other particles outside this range but displaying dimension-related properties may also be considered as nanoparticles [67]. In addition, in terms of pharmaceuticals, particles smaller than 1000 nm have unique physicochemical properties and can still be classified as nanoparticles [68]. Additionally, nanoparticles are a kind of low-toxicity and biocompatible carrier system that is becoming a new strategy for drug delivery to the brain. There are several advantages of nanoparticle delivery systems, such as: (1) biocompatibility and relatively low toxicity; (2) controlled drug release rates; (3) delivery of different types of therapeutic agents, such as nucleic acid-based drugs, peptides, proteins and small molecules; (4) improved pharmacokinetics; and (5) brain-penetrating properties due to their small size and surface modification [67, 69]. Several nanoparticle formulations have recently received FDA approval, further approving their safety and efficacy in a variety of diseases. In addition, nanoparticles need to enter cells effectively, and there are many ways for them to be taken up by cells. Here, we introduce the classification of nanoparticles (Fig. 2), the uptake pathways of nanoparticles in cells and the ways in which nanoparticles act in this section.

3.1 Classification of nanoparticles

3.1.1 *Lipid-based nanoparticles*

Lipid-based nanoparticles are nanovesicles containing at least one lipid bilayer and an empty hydrophilic aqueous inner core, and are a multicomponent lipid system that typically contains phospholipids, ionizable lipids, cholesterol, and polyethylene glycol lipids [70]. Lipid-based nanoparticles are the most common class of nanodrugs approved by the FDA for their many advantages, including (i) simple formulation and self-assembly capability; (ii) good biocompatibility and high bioavailability; (iii) high drug loading ability of hydrophilic and lipophilic cargos; and (iv) controlled physicochemical properties and surface modification to improve blood circulation and regulate biological properties [71, 72].

Lipid-based nanoparticles include a variety of structures, including liposomes, niosomes, transfersomes, solid lipid nanoparticles (SLNs), and emulsions.

(i) Liposomes are traditional and widely used in lipid-based nanoparticles, which are spherical particles made of

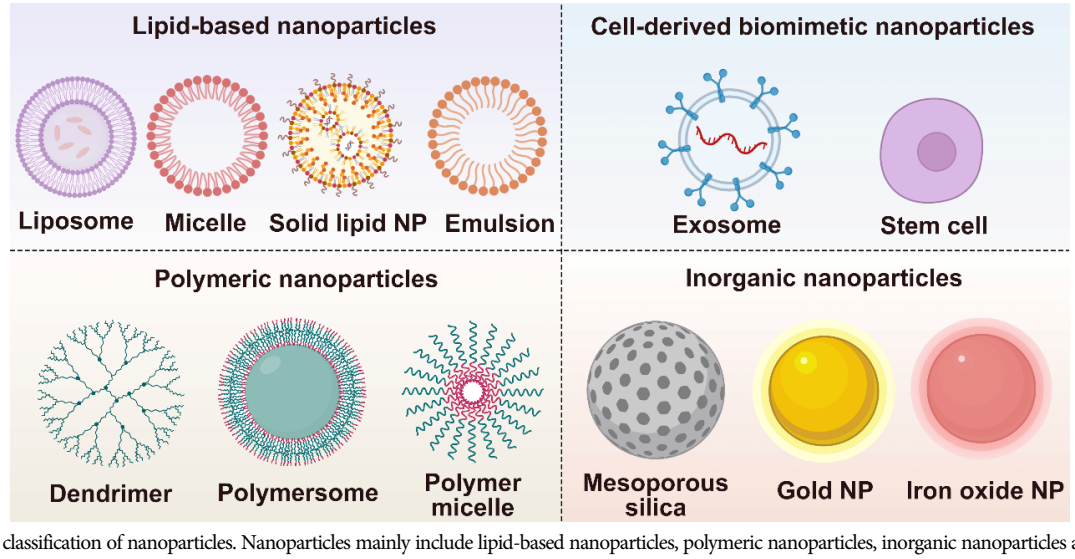

Figure 2 The classification of nanoparticles. Nanoparticles mainly include lipid-based nanoparticles, polymeric nanoparticles, inorganic nanoparticles and cell-derived biomimetic nanoparticles.

phospholipids, cholesterol, and essential oils and consist of a hydrophilic inner core. The size of liposomes ranges from 10 to 1000 nm [73]. The advantages of liposomes include protection of the loaded drugs, a controlled drug release rate, enhanced solubility of hydrophobic drugs, and high bioavailability.

(ii) Niosomes are substitutes for liposomes, and are spherical particles made of cholesterol and nonionic surfactants ranging in size from 10–1000 nm [73]. Compared to liposomes, niosomes have better stability, longer shelf life and more specific targeting [74].

(iii) Transfersomes are spherical particles with size less than 300 nm, and made of phospholipids, cholesterol and edge activators that enhance flexibility and facilitate greater organizational penetration [73]. For lipophilic molecules, transfersomes have high permeability and encapsulation efficiency [75].

(iv) SLNs are spherical particles made of solid fats and surfactants that consist of a solid lipid core and a monolayer lipid, with size range from 50–1000 nm [76]. SLNs have biocompatible and biodegradable components that promote drug uptake by cells and protect drugs in acidic pH environments. Additionally, the process of drug embedding is simple and easy to perform, which is conducive to the promotion of clinical application of SLNs [76].

(v) Lipid emulsions are a kind of lipid material with high drug loading capacity, low toxicity and simple industrial production that are suitable drug carriers for highly lipophilic drugs [77, 78]. Additionally, lipid emulsions can directly separate drugs from body fluids and tissues, reducing the possibility of drug precipitation during intravenous administration. Therefore, lipid emulsions are also suitable carriers for intravenous injection [79].

Lipid-based nanoparticles delivery techniques have been used for drug delivery to the brain. Many natural products have been reported to possess antioxidant, neuroprotective and anti-inflammatory effects, but their application is limited by the fact that individually, they are unstable in biological fluids, rapidly metabolized and unable to cross the BBB [80]. Encapsulation of niacinamide and curcumin in SLN has been shown to significantly improve the bioavailability and efficacy of these natural products in CNS diseases such as AD and PD [81, 82]. Moreover, in animal experiments, nucleic acid-based therapies have been delivered to the brain via surface-modified liposomes [83]. In clinical studies, the liposomal drug formulation Doxil has been shown to be effective in the treatment of glioblastoma [84], and other liposome-based formulations are being investigated for the treatment of Alzheimer's disease [85].

3.1.2 *Polymeric nanoparticles*

Polymer nanoparticles are aggregates of amphiphilic polymers dispersed in the liquid phase with diameters ranging from 1 to 1000 nm [86]. These aggregates contain a core that can encapsulate hydrophobic drugs and a positively charged surface that can adsorb negatively charged gene drugs through electrostatic adsorption. In addition, polymer nanoparticles are biodegradable and can encapsulate small molecules, biological macromolecules and other therapeutic drugs [87]. They can control the release rate of drugs by adjusting the polymer composition and surface properties to promote cell type-specific delivery of therapeutic contents [88, 89]. Additionally, polymer nanoparticles can be prepared from natural materials such as chitosan, alginate, fibrin, and collagen, or synthetic materials such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), and polyethylenimine (PEI). Therefore, a variety of nanoparticles with different characteristics can be prepared through the control of composition [90, 91]. The common synthesis methods for polymer nanoparticles include emulsification, nanoprecipitation, ionic gelation and microfluidic methods [56, 92, 93], and the most common forms of polymer nanoparticles consist of dendrimers, polymersomes and polymer micelles [56].

Dendrimers are nanosized molecules with complex three-dimensional structures and dendritic structure-like branches [94, 95] that have the characteristics of low molecular weight, good biocompatibility and nonimmunogenicity [96–98]. Dendritic polymers can contain many types of drugs, most commonly nucleic acids and small-molecule drugs.

Polymersomes are artificial vesicles composed of a closed bilayer membrane of an amphiphilic block copolymer [99]. Compared with liposomes, they have better membrane stability and drug retention efficiency, and the membrane permeability of polymersomes is conducive to sustainable drug release in the blood circulation [100]. In addition, the chemical diversity of rich block copolymers can better regulate the chemical and physical characteristics of polymersomes so that they can perform a variety of functions better [101].

Polymeric micelles, which are also reactive block copolymers, can self-assemble to form nanospheres with hydrophilic cores and hydrophobic coatings, which help protect water-soluble drugs and increase their circulation time [102]. In addition, polymeric micelles can be loaded with a variety of therapeutic drugs, including small molecules and proteins.

Preclinical evidence suggests that the encapsulation of drugs for the treatment of CNS diseases in PLGA NPs improves pharmacokinetic profiles and drug efficacy in animal models compared to free drug formulations, reducing the required dose or improve side effects. These include galantamine for the treatment of AD [103], tolcapone and resveratrol for anti-PD therapy [104, 105], and chemotherapies such as paclitaxel [106]. Another preclinical study demonstrated that polysorbate 80 and poloxamer 188-coated PLGA nanoparticles significantly improved CNS delivery efficiency [107]. In addition, other surface modifications of polymeric nanoparticles have been shown to increase the delivery of therapeutic cargoes to the brain [108, 109]: for example, combining trans-activated transcriptor (TAT) peptides with polylactic acid nanoparticles significantly increased brain uptake in mice [110].

3.1.3 *Inorganic nanoparticles*

Inorganic nanoparticles, including gold, iron and silicon dioxide, have been widely used for various drug delivery and imaging applications due to their optical, magnetic or electronic properties [111]. In addition, inorganic nanoparticles have a wider surface area and greater drug loading capacity, and are easy to be synthesized and controlled in size. They can also be modified on their surfaces and have antibacterial and antifungal characteristics [112]. Additionally, inorganic nanoparticles can cross the BBB and target disease sites after proper modification of the surface, which is beneficial for the diagnosis and treatment of CNS diseases. Gold nanoparticles (AuNPs) are the most studied type of nanoparticle. They contain gold molecules and range in size from 10 to 100 nm. These materials are widely used in imaging therapy, gene therapy, tumor diagnosis, drug delivery systems, and the treatment of neurodegenerative diseases due to their nonimmunogenicity, biocompatibility, and low toxicity [113]. AuNPs are commonly used in the form of nanospheres, nanorods, nanoshells and nanocages. Additionally, AuNPs are easily functionalized, which is beneficial for targeted drug delivery [114]. Iron oxide nanoparticles are another commonly used inorganic nanomaterial, accounting for the majority of FDA-approved inorganic nanoparticles, and are widely used as contrast agents and drug carriers in preclinical and clinical trials [115]. Mesoporous silica nanoparticles (MSNs) are nanoparticles with a

large surface area, large capacity, porous structure, and easily modified functionalized surface, and their unique structure allows them to encapsulate many different types of drugs [116].

Surgical resection is important in the treatment of gliomas, but radical resection may damage important areas around the tumor. Gao et al. prepared gold nanosphere-based TME-responsive bimodal probes and applied them to magnetic resonance imaging (MRI) and surface-enhanced resonance Raman spectroscopy (SERS) to guide the surgical resection of gliomas, which promoted the use of gold nanosphere imaging agents in clinical medicine [117]. Moreover, a preclinical study used magnetic NPs (Cur-MNPs) composed of superparamagnetic iron oxide nanoparticles coupled to curcumin, which can specifically bind to amyloid plaques, as a diagnostic method for AD [118].

3.1.4 Cell-derived biomimetic nanoparticles

Cell-derived biomimetic nanoparticles provide a new option for drug delivery because they can reduce immunogenicity and prolong cycle time while bypassing the recognition of nanocarriers by mononuclear phagocytes [119].

Exosomes are small membranous vesicles (30–120 nm in diameter) that are naturally occurring nanoparticles. In recent years, exosomes have gradually been developed as a new drug delivery system that can be absorbed by recipient cells. Exosomes can carry nucleic acids, proteins, lipids and metabolites and are involved in important intercellular communication roles. Moreover, they are used as drug and gene carriers for the treatment of CNS disease due to their low immunogenicity, intrinsic stability, high delivery efficiency, and ability to cross the BBB [120]. For example, Yang's team reported that exosomes fused with rabies virus glycoprotein (RVG) and exosomal proteolytic lysosome-associated membrane glycoprotein 2b (Lamp2b) could efficiently deliver the gene drug miR-124 to the sites of cerebral infarction [121], indicating that these exosomes have great potential for clinical application.

Stem cells are undifferentiated cells that can self-replicate and differentiate into a variety of functional somatic cells with multiple therapeutic potential in the treatment of CNS disorders. Various stem cells, including neural stem cells (NSCs) [122], bone marrow-derived stem cells (BMDSCs), mesenchymal stem cells (MSCs) [123], and induced pluripotent stem cells (iPSCs) [124], have been utilized in the study of CNS diseases. Stem cell-based or exosome-based therapies hold promise for the treatment of CNS diseases. However, inadequate delivery to the lesion site, retention time in the lesion and patient tolerance to multidose regimens are three major issues that require further study.

A preclinical study utilized erythrocyte-derived cell membranes encapsulating curcumin-containing PLGA nanoparticles combined with the AD developer T807 to form cell-derived biomimetic nanoparticles, T807/RPCNP-CUR, which can cross the BBB and localize p-tau in neurons for Alzheimer's disease treatment [125].

3.2 Uptake pathways of nanoparticles across the BBB

The uptake pathways of nanoparticles can be divided into passive methods and active methods. Due to the selective permeability of cell membranes, passive diffusion including passive transmembrane diffusion transport and paracellular transport is limited mainly to small uncharged molecules moving along concentration gradients, which limits the delivery of most drugs. Thus, nanoparticles are most often taken up by cells in a way that relies on active transport, including carrier-mediated transcytosis, absorptive-mediated transcytosis and receptor-mediated transcytosis (Fig. 3) [126].

3.2.1 Carrier-mediated transcytosis

Transporters located in the microvasculature of the BBB are carriers for transporting drugs, and these carriers can bind by specific recognition of the drug. Glucose transporters (GLUTs) are important soluble carriers [127] and are highly expressed in mammalian endothelial cells [128]. GLUT1 levels are altered in pathological states, such as in Alzheimer's disease patients, who have reduced levels of GLUT1 in cerebral capillaries, resulting in reduced glucose uptake in the brain and cognitive slowdown. GLUTs may be better carriers of effective neurotherapeutic drugs for neurological disorders and cerebral neurodegenerative diseases. There have been studies using ligand-conjugated nanocarriers, such as multivalent glucoside-coupled liposomes [129], mannose-derived liposomes [130], glucose-coated gold NPs [131], and 2-deoxy-d-glucose functionalized NPs [132], to specifically bind to GLUTs to improve drug penetration across the BBB and thus increase drug levels in the brain.

3.2.2 Absorptive-mediated transcytosis

Positively charged molecules and negatively charged endothelial cell cytoplasmic membranes can overcome the obstructive effect of the BBB through electrostatic interactions and trigger specific transport of drug molecules to the brain. Macromolecular drugs and nanoparticles coupled with cationic ligands can penetrate brain parenchymal tissues with great ease. Absorptive-mediated transcytosis (AMT) of proteins is achieved by cationizing them by amidating their carboxyl groups with natural or synthetic diamines and polyamines [133]. The cationization technique has been applied to the diagnosis and treatment of a variety of

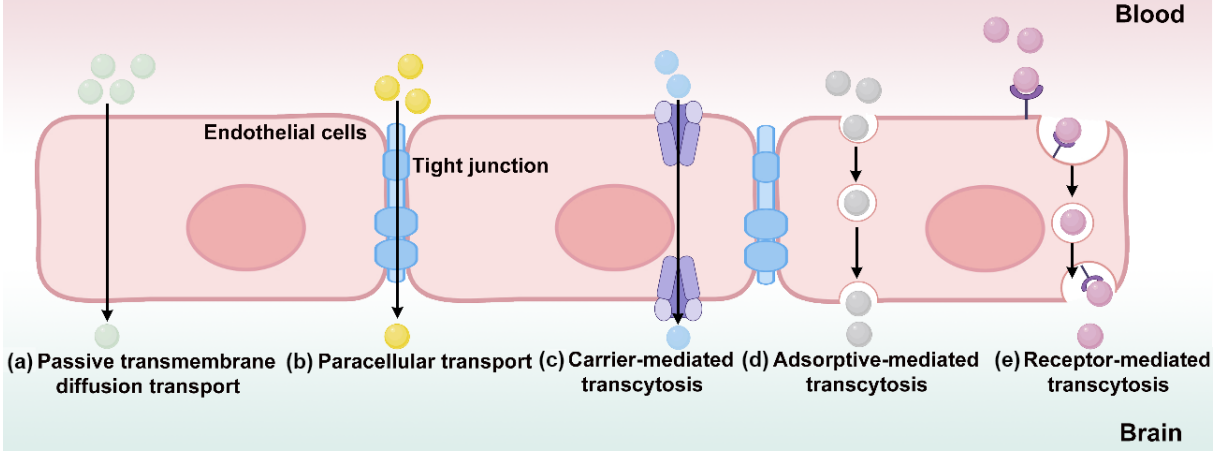

Figure 3 The common uptake pathways of nanoparticles across the BBB. The common uptake pathways of nanoparticles include (a) passive transmembrane diffusion transport, (b) paracellular transport, (c) carrier-mediated transcytosis, (d) absorptive-mediated transcytosis, and (e) receptor-mediated transcytosis.

proteins, such as albumin [134], anti-amyloid peptide antibodies [135], and nerve growth factor [136]. In addition, the strategic application of cell-penetrating peptides (CPPs) in the endothelial transport of hydrophilic neuropharmaceuticals utilizes nonreceptor-mediated endocytosis. CPPs are cationic peptides that bind to the anionic cell membranes of the microvascular endothelium to transport drugs and genes to specific sites in the brain [137]. In the last decade, CPPs have been widely used to successfully deliver potential therapeutic drugs to the brain. For example, compared with unmodified DOX, SynB, a peptide derived from a natural protein, significantly enhanced the brain uptake of DOX by inhibiting P-gp-mediated efflux [138].

3.2.3 *Receptor-mediated transcytosis*

Many types of receptors are present in endothelial cells at the BBB, including transferrin receptor (TfR), insulin receptor, low-density lipoprotein receptor (LDLR), leptin receptor, and many others, which are able to bind to ligands and thereby trigger receptor-mediated transcytosis, facilitating drug crossing of the BBB and targeting to the brain [139]. For example, Tf can be coupled to the surface of nanoparticles to target endothelial cells via TfRs [140]. However, endogenous Tf competes with exogenous Tf for binding to TfRs, resulting in poor targeting efficiency of the delivery system [139]. Lf, another glycoprotein of the Tf family, competes less with endogenous Lf and binds to the Lf receptor on brain capillary endothelial cells, as well as having a binding affinity for LRP1 and LRP2 expressed in the brain [141], which are effective ligands for nanoparticles to enter the brain. In neurodegenerative diseases, LRP-mediated transcytosis is an obvious pathway for transporting Lf from the circulation through endothelial cells, which can facilitate drug delivery in the treatment of neurological diseases and brain tumors [142].

3.3 The ways in which nanoparticles act

Nanoparticles play a role in CNS diseases in different ways, including as carriers, as targeted delivery systems, and as immunomodulators (Fig. 4).

3.3.1 *As carriers*

Normally, nanoparticles are used as carriers for drugs, such as gene therapy drugs, chemotherapeutic drugs and other small molecule drugs. For example, lipid-based nanoparticles are used to encapsulate hydrophilic and hydrophobic drugs, including nucleic acids, peptides, and proteins [3]; gold nanoparticles are able to bind to a wide range of molecules and thus deliver a wide range of therapeutic drugs, from antibiotics to DNA [3].

3.3.2 *As targeted delivery systems*

Surface-modified nanoparticles deliver drugs precisely to the target. Typically, one or more targeted parts are used on the surface of nanoparticles so that they can bind to specific receptors on the BBB or receptors specifically expressed in brain tumors, thereby increasing the concentration of the drug at the intended target site and reducing exposure to nontarget organs. For example, surface modification of polylactic acid-coglycolic acid (PLG) nanoparticles with rabies virus glycoprotein (RVG29) increased the residence time and exposure time of drug-coated nanoparticles in the CNS compared to those of nontargeted nanoparticles [143]. Additionally, the intravenous delivery of folate receptor alpha-folic acid (FRα-FA)-modified polymer nanoparticles promoted greater accumulation of their loaded drugs in the brain, demonstrating the ability of surface-modified nanoparticles to target active molecules from systemic circulation to the CNS [144]. Therefore, proper modification of the surface of nanoparticles can help deliver drugs to the target accurately and enhance the efficacy of drugs.

3.3.3 *As immunomodulators*

The immune system is trained to protect the body by eliminating cancer cells, viruses, pathogens, etc., but certain genetic traits allow harmful substances to escape and suppress immune cells. Therefore, enhancing the uptake of drugs or pathogens by antigen-presenting cells (APCs) to enhance the response of T cells is the key to treating disease, and immunomodulators are needed in this process. Nanoparticles can be used to modulate immune activation or immune suppression. For example, in cancer therapy, nanoparticles can sensitize cancer cells to therapeutic drugs, thereby increasing the body's response to the implemented precision therapy [145]. Simultaneously, in cancer vaccines, where tumor-derived antigens are used for immunization, the use of nanoparticles can protect antigens from degradation and increase the uptake of antigens by APCs, thus initiating and activating T cells to play an immune role. Nanoparticles can also significantly improve the delivery of therapeutic drugs by protecting against immunotherapy and enhancing their interaction with immune cells. As with other applications, the structure of nanoparticles and

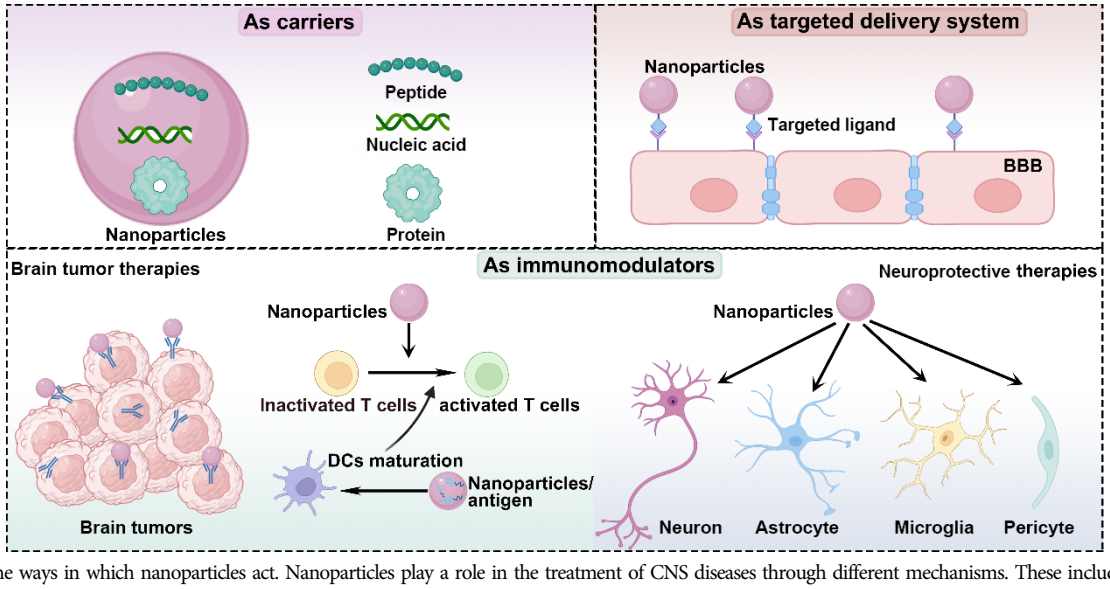

Figure 4 The ways in which nanoparticles act. Nanoparticles play a role in the treatment of CNS diseases through different mechanisms. These include carriers of drugs such as peptides, nucleic acids and proteins; modification of targeted drugs to enhance the ability to penetrate the BBB; immunomodulators, which play a therapeutic role in brain tumors; and neuroprotective therapies for neurodegenerative diseases.

active targeting can influence cell uptake, antigen presentation, and the intensity of the immune response [146].

In addition, current research on CNS immunomodulation has focused on inflammation associated with AD, PD and MS. In neurodegenerative diseases, the concerns of neuroprotective therapies include neurons, astrocytes, pericytes, endothelial cells and other neuronal cells, and their alterations in antioxidant enzymes, antiapoptotic pathways and downstream cytokines [147, 148]. The activation of T cells by nanoparticles has become a targeted therapy used to reduce chronic inflammation [149]. On the one hand, nanoparticles themselves have a therapeutic effect on neuroinflammation. For example, AuNPs can induce microglial polarization toward the neuron-regenerative M2-like phenotype [150]. On the other hand, nanoparticles can be involved in neuroinflammation as carriers of therapeutic drugs such as curcumin, okadaic acid, quercetin, anthocyanin, levodopa and others [151]. With the help of nanoparticles, drugs can more easily cross the BBB to reach the target cells and synergize with T cells through positive feedback regulation to jointly inhibit inflammatory pathways and the release of inflammatory cytokines [151].

4 Distribution of nanoparticles

4.1 Main delivery routes of nanoparticles

Drugs, including nanoparticles for the treatment of CNS injury, can reach brain lesions mainly through oral or invasive routes, including convection-enhanced delivery (CED), intrathecal administration, and noninvasive routes, such as intranasal administration. Here, we summarize the delivery routes of these nanoparticles (Fig. 5).

4.1.1 Systemic administration

Intravenous administration is an administration method that involves rapid onset, high drug bioavailability, and avoidance of first-pass metabolism in the liver and is especially useful in emergency situations. Additionally, intravenous administration can introduce many types of treatment through the blood into the circulatory system, leading to systemic delivery to the CNS. Systemic administration of drugs for CNS diseases is common but clinically limited, mainly due to the presence of the BBB, which prevents more than 98% of small molecules with molecular weights less than 500 Da and nearly 100% of molecules with molecular weights greater than 500 Da from entering the brain [152]. Therefore, the development of new carriers with the ability to cross the BBB is key for systemic administration.

4.1.2 Invasive local administration

Direct delivery of therapeutic drugs into the brain by invasive means can ensure a high concentration of drugs in brain lesions and reduce systemic toxicity [153]. In the surgical treatment of malignant tumors, subarachnoid hemorrhage, PD, or traumatic injury, invasive local administration is often a viable strategy [1].

For example, CED is an invasive drug administered that relies on the continuous application of positive pressure through a pump and the direct injection of drugs into the lesion site by a catheter. Additionally, CED can bypass the BBB and directly deliver drugs to the specified lesion site efficiently and accurately [154]. A variety of factors affect the tissue distribution of drugs in vascular ECs after they reach lesions through CED, including (1) the properties of the drugs themselves, such as half-life and tissue binding properties; (2) the drug flow rate and volume during administration; (3) the size, shape and position of the cannula used for CED; and (4) catheter-induced tissue damage and influence of drug reflux near the catheter [155, 156]. In Zhan's study [157], the efficacy of doxorubicin-coated liposomes for the treatment of brain tumors via CED was investigated under different conditions. The results showed that intracerebral infusion could effectively improve the flow rate of interstitial fluid at the infusion site and inhibit blood leakage around the infusion site. Moreover, by increasing the concentration and infusion rate of liposome solution, liposome administration to tumors with normal microvascular density or liposomes with low vascular

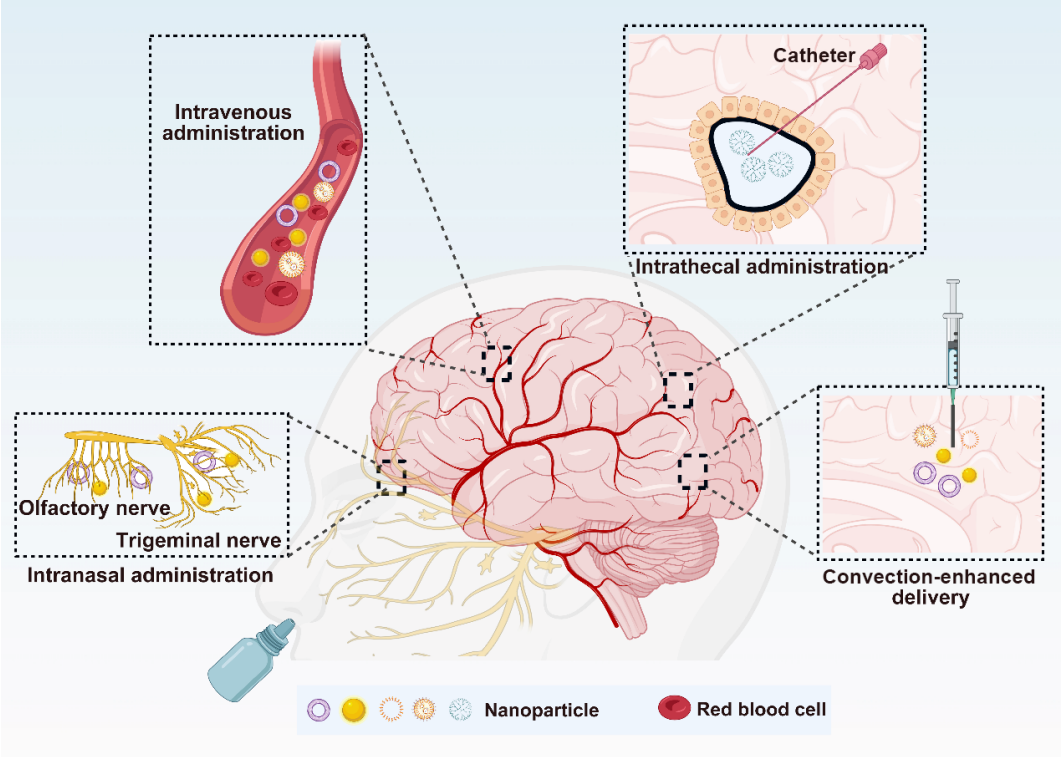

Figure 5 The delivery routes of nanoparticles to the CNS. The main delivery routes of nanoparticles in the CNS include systemic administration, such as intravenous administration; invasive routes, including CED and intrathecal delivery; and noninvasive routes, such as intranasal administration.

permeability can improve the therapeutic effect. The results of this study could be used to improve treatment options involving CED. In Zhang's study [158], the use of CED for brain penetrating nanoparticles loaded with cisplatin was shown to reduce the inherent toxicity associated with cisplatin and simultaneously increase the concentration of cisplatin in tumors, thus improving therapeutic efficacy.

Intrathecal administration is a direct method of administration to the cerebrospinal fluid that bypasses the BBB. This method of administration can achieve high doses of drugs in the brain, reduce drug loss and the risk of off-target exposure, as well as toxicity to other sites [159]. However, ependymal cells in the choroid plexus also act as barriers to drug action, limiting tissue abduction. Therefore, nanoparticles and other materials are being integrated to improve nanoparticle delivery and brain tissue penetration [160].

4.1.3 *Noninvasive administration*

Intranasal administration is a noninvasive and simple treatment route for CNS diseases. The nasal cavity is close to the brain and can be connected to nerves, leading to the brain. Therefore, nanoparticles administered through the nasal cavity can bypass the BBB and the blood-cerebrospinal fluid barrier to reach brain lesions directly [161]. After entering the nasal cavity, the nanoparticles quickly enter the brain mainly through the trigeminal nerve pathway and the olfactory pathway. Due to the abundant blood vessels in the nasal cavity, some of the nanoparticles are also absorbed through the systemic pathway [162, 163]. However, due to the limited structure of the nasal cavity, only a small dose is absorbed in this way. The presence of cilia and enzymes in the nasal cavity is also an obstacle to the further introduction of nanoparticles into the brain [164]. However, nanoparticles modified with polymers such as chitosan, PLGA and PLA can reduce the obstruction of cilia and achieve greater access to the brain [165]. In addition, intranasal administration of drugs may cause irritation and damage to the nasal mucosa, and corresponding modifications of nanoparticles can effectively protect the nasal mucosa and reduce side effects.

4.2 Factors affecting the distribution of nanoparticles

The physicochemical and mechanical properties of nanoparticles, such as their size, morphology, surface charge, hydrophilicity, stiffness and surface modification, have a profound effect on their cycle time in the body (Fig. 6). Increasing the circulating half-life of nanoparticles *in vivo* is an important condition for nanoparticles to continuously cross the BBB and is one of the key directions of research in this field.

4.2.1 *The size of the nanoparticles*

From the perspective of the toxicological characteristics of nanoparticles, the size of nanoparticles plays an important role in various applications. Several studies have shown that nanoparticles larger than 20 nm can cross the BBB. However, very small nanoparticles less than 5 nm in length are easily excreted by the kidneys and cleared by the target tissue, and nanoparticles larger than 200 nm are easily removed or ingested by other organs, thus affecting drug distribution and possibly causing adverse effects on other organs [166]. In general, nanoparticles larger than 200 nm are thought to be easier to be removed than other nanoparticles. However, larger nanoparticles can carry more drugs, reducing the amount of drugs used. In addition, it has been estimated that the size limit of the diffusion of nanoparticles in the extracellular space of the brain is less than 114 nm. Studies in rodents have confirmed that nanoparticles smaller than 100 nm are most suitable for systemic delivery to the brain [167]. From the perspective of the uptake efficiency of nanoparticles, the cellular uptake of nanoparticles is affected by their size. In one study, gold nanoparticles with diameters of 14, 30, 50, 74, and 100 nm were used to observe the effect of different sizes of nanoparticles on the cellular uptake efficiency of HeLa cervical cancer cells. The results showed that the gold nanoparticle size of 50 nm achieved the highest uptake efficiency, which indicated that cell uptake is influenced by nanoparticle size [168]. Therefore, it is important to find and prepare suitably sized nanoparticles to escape clearance from the lung, liver, spleen, and kidney and to effectively reach brain lesions.

4.2.2 *The morphology of the nanoparticles*

The different morphologies of nanoparticles affect their biological distribution. Nonspherical nanoparticles have "cell avoidance" properties, and the morphology of nanoparticles also affects their circulation in the body, which may influence the necessary doses and the efficacy of nanoparticle-based therapies [166]. In addition, shape determines the adhesion pattern of nanoparticles, thus altering the uptake efficiency of nanoparticles by target cells. For example, nanorods (rod-shaped nanoparticles) have been shown to enter cells more efficiently than spherical particles of the same volume in a microfluidic *in vitro* BBB model [169]. However, PEG-modified gold nanorods are less easily absorbed by macrophages than nanospheres [170], which indicates that different nanoparticle morphologies also affect the efficiency of cellular uptake of nanoparticles and the efficacy of the drugs they carry. The morphology of nanoparticles, including nanorods, nanospheres, and nanocrystals, inspires a variety of ideas for developing materials for delivering drugs to the brain.

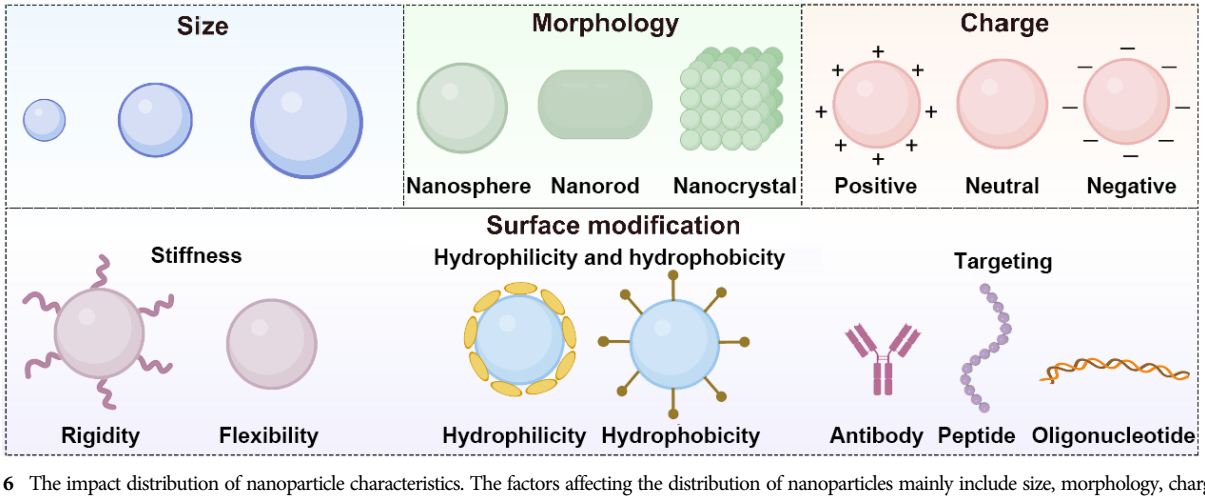

Figure 6 The impact distribution of nanoparticle characteristics. The factors affecting the distribution of nanoparticles mainly include size, morphology, charge, and surface modification.

4.2.3 The surface charge of the nanoparticles

The surface charge of nanoparticles determines their cellular uptake and biological distribution, and affects their effectiveness in participating in immune responses [171, 172]. Normally, a positively charged nanoparticle increases the endocytosis of the cell by enhancing the electrostatic interaction with the negatively charged cell membrane, which makes it easier for the cell to internalize compared with a neutral or negatively charged nanoparticle [173]. Kim's team used gold nanoparticles carrying fluorescein *in vitro* in a 3D model and found that positively charged nanoparticles were more significantly absorbed by proliferating cells, while negatively charged nanoparticles spread more rapidly in tumor columns [174]. On the other hand, the positively charged liposome itself can act as a "danger signal" that can evoke immunity, especially through the proinflammatory cascade [175]. Moreover, positively charged nanoparticles are more readily taken up by macrophages and dendritic cells (DCs), and induce DCs to mature and participate in immunomodulation [173]. In addition, positively charged nanoparticles carrying antigens improved antigen transport to APCs and produced more cytotoxic T-lymphocyte responses than antigens from nucleic acid classes, such as DNA alone [176]. However, permanently positively charged nanoparticles may be toxic and ineffective, but this deficiency can be compensated by modifying the surface charge of nanoparticles [175]. These results suggest that researchers could consider the different effects of surface charge on biological distribution when designing nanoparticles to treat diseases.

4.2.4 Surface modification of nanoparticles

Surface modification and cloaking techniques can help nanoparticles bypass identification and removal systems which can lead them to rapid removal and instability. It has been reported that nanoparticles with rigid copolymer ligands have a better ability to pass through the cell membrane [177]. Therefore, to improve the robustness of softer nanoparticles, auxiliary lipids, cholesterol, and pegylated lipids can be added to lipid-based nanoparticles to increase their stability, while in polymer nanoparticles, cross-linking techniques can be utilized [178, 179].

Many studies have shown that the hydrophobicity of the nanoparticle surface also affects its uptake and immune activation by APCs. As the hydrophobicity of the nanoparticles increases, their ability to be internalized by cells and the production of costimulatory markers, including CD86, in DCs also increase [180]. For example, in mouse splenocytes, proinflammatory cytokine gene expression increased with increasing hydrophobic positively charged nanoparticles [181]. In addition, Moyano et al. utilized different types of surface-modified gold NPs to modulate the hydrophobicity of NPs. It was reported that the degree of hydrophobicity was positively correlated with the production of inflammatory cytokines, including tumor necrosis factor (TNF) [181].

In addition, different modifications on the surface of nanoparticles will affect their targeting *in vivo*. Specific cell targeting is achieved by modifying the surface of nanoparticles with ligands. The ligand molecule can selectively or specifically recognize the presence of another molecule in the target cell, such as the receptor. Antibodies are a class of general-purpose ligands because they target specific antigens. Additionally, other types of proteins, such as peptides, aptamers, oligonucleotides and small molecules, such as folate or carbohydrates, can also be used as ligands [182]. Among them, peptides can recognize specific receptors, such as integrins of arginine-glycine-aspartate (RGD) peptides, that target tumors [183]. Cell-penetrating peptides, such as the T7 peptide, which is a brain-targeting heptapeptide with a high affinity for the TfR overexpressed on glioma cells, are often modified into liposomes to form brain-targeting lipid-based nanoparticles to deliver drugs to the brain [184]. Therefore, the search for suitable materials to modify the surface of nanoparticles will enhance their targeting ability and increase the availability of drugs.

4.3 The clearance of nanoparticles

After drugs enter the body through different routes, such as oral, intravenous, and intranasal administration, they may be cleared by the body due to the different properties of the drugs. Typically, before therapeutic drugs reach the brain, nanoparticles with diameters smaller than 10 nm are usually cleared rapidly by the kidneys, and nanoparticles with diameters larger than 200 nm are often at risk of activating the complement system [62]. Polymeric nanoparticles may accumulate in the liver or be taken up by the reticuloendothelial system, leading to rapid clearance of the drug from the circulation, resulting in a decrease in the therapeutic effect [185]. In terms of charge, positive nanoparticles are usually removed the fastest, followed by negative nanoparticles, while neutral and slightly negative nanoparticles have the longest half-life in circulation [54, 58]. Increased clearance and decreased distribution may require higher and/or more frequent dosing, which may have undesirable consequences both in terms of safety and in practical application.

A prolonged circulating half-life of a drug is a prerequisite for systemic and sustained drug entry into the BBB. Therefore, the use of nanoparticles that are not cleared immediately after administration is prioritized in the treatment of CNS diseases. Nanoparticles with diameters smaller than 100 nm, high aspect ratios, or near neutral charges are suitable for use in the treatment of CNS diseases [186]. Further *in vivo* studies in rodents have shown that nanoparticles smaller than 100 nm are best suited for delivery to the brain via the systemic delivery route [167, 187]. In addition, surface modification and stealth techniques allow nanoparticles to avoid systems that may lead to rapid degradation or removal of the nanoparticles. For example, excipients such as helper lipids, cholesterol and polyethylene glycolated lipids [178, 188] can be formulated with lipid-based nanoparticles to increase their stability, whereas polymeric nanoparticles can use cross-linking techniques to enhance their stability [179, 189]. In conclusion, designing nanoparticles that are safe, have therapeutic effects and can avoid rapid clearance by the body is important.

5 Clinical application of nanoparticles in CNS diseases

5.1 Lipid-based nanoparticles

In a phase I/II study conducted by Sabine Mueller's team [190], liposomes containing soluble panobinostat (MTX110) were tested for their ability to inhibit tumor growth and angiogenesis in diffuse intrinsic pontine glioma (DIPG) (Table 1). Additionally, CED technology has been applied to directly overcome the BBB so that drugs can directly reach the tumor site and have enhanced efficacy.

The cellular matrix protein in human cytomegalovirus phosphoprotein 65 (pp65) is a highly sensitive and specific antigen for glioblastoma multiforme [191], and DCs are specialized APCs that are required for the activation of T-cell-mediated immune responses. Based on these findings, autologous total tumor mRNA and pp65 full-length (fl) lysosomal-associated membrane protein (LAMP) mRNA-loaded DOTAP liposome vaccines were used to activate DCs *in vivo* by intravenous injection to generate a strong

Table 1 The clinical application of lipid-based nanoparticles in treating CNS diseases

Disease	Drug	Phase	Delivery route	Status	NCT number[a]	Application
DIPG	MTX110	Phase I/II	CED	Completed	NCT03566199	Treatment
Glioblastoma	RNA-LPs	Phase I	Intravenous	Recruiting	NCT04573140	Treatment
Brain metastases	DepoCyte®	Phase I	Intrathecal	Completed	NCT00854867	Treatment
Meningeal metastasis of breast cancer	DepoCyte®	Phase III	Intrathecal	Completed	NCT01645839	Treatment
Brain tumor	Doxorubicin	Phase I	Intravenous	Completed	NCT00019630	Treatment
Brain metastases	Irinotecan	Phase II	Intravenous	Recruiting	NCT05255666	Treatment
Brain metastases	Doxorubicin	Phase II	Intravenous	Terminated	NCT00465673	Treatment
Meningeal neoplasms	Cytarabine	Phase IV	Intrathecal	Completed	NCT00029523	Treatment
Brain tumors	Vincristine	Phase I	Intravenous	Completed	NCT01222780	Treatment
Cryptococcal meningitis	Amphotericin	Phase II	Intravenous	Recruiting	NCT03945448	Treatment
AD	ADx-001	Phase I	Intravenous	Recruiting	NCT05453539	Treatment
Central nervous system metastases tumors	Cytarabine	Phase II	Intrathecal	Completed	NCT00992602	Treatment

[a]NCT: National clinical trial.

immune response for the treatment of glioma. A clinical phase I trial is currently recruiting patients.

In a phase II clinical trial conducted by Mrugala's team [192], three patients diagnosed with leptomeningeal carcinomatosis were enrolled and treated with a median dose of high-dose methotrexate (HD-MTX) by intravenous injection and liposomal cytarabine by intrathecal administration three times each, and the longest surviving patient received 5 doses of HD-MTX and 4 doses of intrathecal liposomal cytarabine. The results of the trial showed that the protocol was well tolerated, with no obvious hematotoxicity or signs of neurotoxicity, except for grade 4 lymphocytopenia in one patient.

Similarly, in a phase III clinical trial, Emilie Le Rhun's team [193] used liposomal cytarabine plus systemic therapy to treat leptomeningeal metastasis (LM) from breast cancer by intrathecal injection. In their trial, the median progression-free survival (PFS) was 2.2 months in the control group (systemic therapy alone) versus 3.8 months in the experimental group (systemic therapy plus intrathecal liposomal cytarabine), and the median overall survival was 4.0 months in the control versus 7.3 months in the experimental group. These findings showed that the addition of intrathecal liposomal cytarabine to systemic treatment could improve LM-related PFS. This finding demonstrates the feasibility of intrathecal drug delivery and the need for more effective drugs for the treatment of this disease.

5.2 Polymeric nanoparticles

Carmustine (BCNU) is a chemotherapeutic drug that can inhibit the proliferation of tumor cells by cross-linking DNA, and Gliadel, a biodegradable polymer wafer containing BCNU, is a direct implantation method for delivering chemotherapeutic drugs to lesions during surgical resection of tumors [194] (Table 2). Studies have shown that Gliadel can maintain a high concentration of chemotherapeutic drugs in lesions for approximately 3 weeks after implantation [195]. As a result, wafers are increasingly being used for local administration in the treatment of primary and metastatic brain tumors. In a trial, the Gliadel wafer was implanted into patients undergoing recurrent glioblastoma multiforme surgery, and the results showed that the implantation of the Gliadel wafer could improve patients' median survival (5.4 months) compared to that of patients receiving placebo and undergoing initial glioblastoma multiforme resection (7.2 months) [196]. Moreover, Gliadel improved total survival time (9.2–13.4 months).

5.3 Inorganic nanoparticles

In a phase I trial conducted by Camille Verry's group [197], they used a novel gadolinium-based nanoparticle, AGulX, a sub-5 nm nanoparticle composed of a polysiloxane matrix and a gadolinium chelate, to evaluate the safety and maximum tolerated dose of AGulX for intravenous administration in combination with whole-brain radiotherapy in patients with brain metastases (Table 3). Five concentrations of AGulX nanoparticles were administered intravenously at 15, 30, 50, 75 or 100 mg/kg, with three patients in each group. When AGulX reached 100 mg/kg, no dose-limiting toxicity was observed. Additionally, effective metastasis targeting (T1 MRI enhancement, tumor selectivity) and persistent AGulX enhancement were observed in metastases from patients with primary melanoma, lung cancer, breast cancer, or colon cancer. In metastases, the concentration of AGulX after administration was proportional to the injected dose. Additionally, clinical benefit was observed in 13 of 14 evaluable patients with stable or reduced tumor volume. MRI analysis revealed a significant correlation between contrast enhancement and tumor response, thus supporting a radiosensitization effect. In conclusion, this clinical trial showed that AGulX combined with radiotherapy is safe and feasible for the treatment of brain metastases, ongoing phase II studies will evaluate its efficacy more definitively.

Table 2 The clinical application of polymer-based nanoparticles in treating CNS diseases

NP types	Disease	Drug	Phase	Delivery route	Status	NCT number	Application
Dendrimer	ALS[a]	18F-OP-801	Phase I	Intravenous	Not yet recruiting	NCT05395624	Diagnostic
Polymers	Brain metastases	Carmustine implants	Phase II	Surgical implants	Completed	NCT00003878	Treatment
Polymers	Brain and central nervous system tumors	Carmustine implants	Phase I	Surgical implants	Completed	NCT00003876	Treatment
Polymers	Peripheral nerve injury	Polyethylene glycol (PEG)	Phase I	Surgery	Recruiting	NCT02359825	Treatment
Polymers	Glioblastoma	Carmustine wafer	Phase I/II	Surgical implants	Withdrawn	NCT00984438	Treatment

[a]ALS: amyotrophic lateral sclerosis.

Table 3 The clinical application of inorganic nanoparticles in treating CNS diseases

NP types	Disease	Drug	Phase	Delivery route	Status	NCT number	Application
Iron oxide	Multiple sclerosis	Ferumoxytol	Phase I	Intravenous	Completed	NCT02511028	Diagnostic
Iron oxide	Multiple sclerosis	Ferumoxytol Gadoteridol	Early phase I	Intravenous	Recruiting	NCT05357833	Diagnostic
Silica particle	Brain cancer Pituitary adenoma	89Zr-cRGDY	Phase I	Intravenous	Recruiting	NCT03465618	Diagnostic
Silica particle	Brain tumors	124I-labeled cRGDY	Not applicable	Intravenous	Active, not recruiting	NCT01266096	Diagnostic
Gadolinium	Brain metastases	AGuIX®	Phase II	Intravenous	Recruiting	NCT03818386	Treatment
Gadolinium	Brain tumor	AGuIX	Phase II	Intravenous	Recruiting	NCT04899908	Treatment
Gadolinium	Brain metastases	AguIX	Phase I	Intravenous	Completed	NCT02820454	Treatment
Gadolinium	Brain metastases	AGuIX	Phase II	Intravenous	Terminated	NCT04094077	Treatment
Gold	Glioblastoma	NU-0129	Early phase I	Intravenous	Completed	NCT03020017	Treatment
Gold	PD	CNM-Au8	Phase II	Oral	Completed	NCT03815916	Treatment
Gold	Multiple sclerosis	CNM-Au8	Phase II	Oral	Recruiting	NCT03993171	Treatment
Gold	ALS	CNM-Au8	Phase II	Oral	Completed	NCT04098406	Treatment

In a phase II trial conducted by Steve Vucic's group [198], they designed a novel nanodrug, CNM-AU8, as a therapeutic intervention to enhance the metabolic and energy capacity of motor neurons. CNM-AU8 is an aqueous suspension of clean surface, multifaceted gold nanocrystals with extraordinary catalytic capabilities that can increase the efficiency of key metabolic reactions while reducing the level of reactive oxygen species. In this trial, patients will be randomized 1:1 to receive 30 mg of CNM-AU8 orally once daily or a matched placebo during 36 weeks of double-blind treatment. Efficacy will be assessed by changes in motor neuron loss measured by electromyography. Additionally, phase II clinical trials of CNM-AU8 in PD and multiple sclerosis are underway.

5.4 Cell-derived biomimetic nanoparticles

In a clinical trial [199], investigators compared the efficacy of cell-derived biomimetic nanoparticles (MSC therapies) in patients with multiple sclerosis (MS) following the intravenous (IV) or intrathecal (IT) administration of mesenchymal stem cells (MSCs) (Table 4). Among the 48 patients with progressive multiple sclerosis, significantly fewer failed treatments were observed for patients in the MSC-IT and MSC-IV groups than those in the sham treatment group (6.7%, 9.7%, and 41.9%, respectively; P = 0.0003 and P = 0.0008). At the 1-year follow-up, 58.6% and 40.6% of patients treated with MSC-IT and MSC-IV, respectively, showed no signs of disease activity. Treatment with MSCs was well tolerated in patients with progressive MS and induced short-term beneficial effects at the primary endpoint, suggesting the feasibility of stem cell-based therapeutic modalities in clinical applications.

6 Challenges and conclusion

Drug delivery to the CNS remains technically and clinically challenging due to the presence of the BBB, and the selection of appropriate delivery modes and delivery vehicles requires more precise combinations and multiple attempts to determine the optimal combination. Combining multiple routes of administration, such as noninvasive intranasal administration, invasive CED administration and intravenous administration, may provide temporal and multifaceted control of CNS therapies, thus further improving efficacy. However, animal experiments typically use rodents, which limits the probability of success in subsequent preclinical studies and human clinical trials. Therefore,

Table 4 The clinical application of cell-derived biomimetic nanoparticles in treating CNS diseases

NP types	Disease	Drug	Phase	Delivery route	Status	NCT number
Exosomes	Epilepsy	GD-iEXo-002	Early phase I	Intranasal	Recruiting	NCT05886205
Exosomes	Neurodevelopmental disorders Hypoxia-ischemia	Exosomes	Not applicable	Intranasal	Not yet recruiting	NCT05490173
Exosomes	Ischemic stroke	GD-iExo-003	Phase I	Intravenous	Not yet recruiting	NCT06138210
Exosomes	Cerebrovascular disorders	Exosomes	Phase I/II	Intraparanchymal	Unknown	NCT03384433
Exosomes	AD	MSCs-Exos	Phase I/II	Intranasal	Unknown	NCT04388982
Stem cells	Ischemic stroke	MultiStem	Phase III	Intravenous	Recruiting	NCT03545607
Stem cells	Ischemic stroke	MSCs	Phase III	Intravenous	Unknown	NCT01716481
Stem cells	Spinal cord injury	MSCs	Phase II	Intrathecal	Recruiting	NCT04520373
Stem cells	Neonatal stroke	MSCs	Phase I/II	Intranasal	Completed	NCT03356821
Stem cells	Neonatal stroke	MSCs	Phase I/II	Intranasal	Completed	NCT03356821
Stem cells	Ischemic stroke	UC-MSCs[a]	Phase I/II	Intranasal	Recruiting	NCT05008588
Stem cells	PD	MSCs	Phase II/III	Intranasal/Intravenous	Unknown	NCT04146519
Stem cells	Multiple sclerosis	MSCs	Phase II	Intrathecal/Intravenous	Completed	NCT02166021
Stem cells	Multiple sclerosis	HSCs[b]	Phase III	Intrathecal/Intravenous	Recruiting	NCT04047628
Stem cells	AD	BMSCs	Not applicable	Intranasal/Intravenous	Enrolling by invitation	NCT03724136

[a]UC-MSCs: umbilical cord mesenchymal stem cells; BMSCs: bone narrow stem cells; [b]HSCs: hematopoietic stem cells.

it is challenging to develop a suitable animal model that can be used on a large scale.

The BBB prevents the unregulated exchange of neuroimmune substances and immune cells between the CNS and the blood. Whereas dysfunction of the BBB may occur in conjunction with systemic and neuroinflammatory changes, a healthy and intact BBB has a relatively greater ability to resist dysfunction caused by peripheral inflammatory injury. Thus, the integrity of the BBB is an important part of maintaining a relatively stable immune microenvironment in the brain [200, 201]. Currently, various nanoparticles, such as lipid-based nanoparticles, cell-derived biomimetic nanoparticles, inorganic nanoparticles, polymeric nanoparticles, and other delivery vehicles, are playing an increasingly important role in overcoming the BBB for the treatment of CNS disorders. However, nanoparticles still have limitations in the treatment of CNS disorders: their safety, efficacy, and regulatory issues are the main challenges faced by nanoparticle drugs for the clinical treatment of CNS disorders. Nanoparticles are potentially neurotoxic in the CNS, with the main adverse effect being an increase in oxidative stress, including the production of hydrogen peroxide, malondialdehyde, and nitric oxide [202]. In addition to the risk of clearance of drugs delivered into the brain by nanoparticle delivery systems that bypass or cross the BBB, inflammatory and allergic reactions may occur, and interactions with the immune system are key to the therapeutic efficacy. Additionally, nanoparticles cause local immune response inflammation, thereby increasing the levels of proinflammatory cytokines and chemokines such as TNF-α, IL-β and IL-6 [203]. Moreover, the interaction between the nanoparticle delivery system and the immune system to carry out therapy is also a therapeutic strategy. For example, immunotherapy using liposomes can stimulate the desired immune response, resulting in a more specific and effective effect [204, 205]. The potential long-term adverse effects of nanoparticles on the CNS are poorly studied, which is a concern considering the possibility that successful delivery of nanoparticles to the brain parenchyma is expected to be long-lasting.

Additionally, the gap that exists between the industrial acceptance and clinical translation of nanoparticle drugs is a challenge. Researchers are working toward addressing the practical issues involved in the development of nanoparticle drugs as well as the preclinical, clinical and pharmaceutical aspects so that research can be translated from academia into products for industry and medicine.

In conclusion, the technical challenges of CNS drug delivery are gradually being overcome, and the prospects for continued progress and material development are promising.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 82073366 and 32100748), the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYGD18007), and the National Natural Science Foundation of Sichuan Province (No. 2022NSFSC1642). All figures were made by Biorender.

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