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Application of Novel Drug-Delivery Strategies in Neurological Disorders

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Neurological disorders are the leading cause of global health loss and disability. However, the success rate of drug development in the nervous system is very low, mainly because of the blood-brain barrier (BBB). In addition, gastrointestinal irritation, low stability, rapid metabolism, imprecise targeting, and organ toxicity of drugs are also important constraints in the development and application of neurological drugs. Emerging technologies, such as nano-delivery technology, offer a number of strategies to address these challenges drugs face entering the central nervous system. This review systematically introduces the various challenges of existing drug development in neurological disorders and summarizes BBB regulation strategies, drug delivery strategies, and modes of administration. It's summarized that the challenges of BBB can be addressed with the help of strategies including physical stimulation and modification of nanocarriers, and drug delivery in the nervous system can be achieved with the help of passive and active nanocarriers and self-assembly. Moreover, drug delivery strategies in major neurological disorders are discussed in detail. Finally, the limitations of some drug delivery strategies are summarized and the future development direction is prospected, which can provide new ideas and technologies for the optimization of drug delivery for neurological disorders.

1. Introduction

Neurological disorders (ND), such as stroke, Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, and brain tumors, are a class of diseases that pose a serious risk to human health. It is estimated that there were 805.17 million neurological disorder cases in 2019, demonstrating the enormous public health impact of ND. The incidence of ND will increase further with the aging of the global population and the increase in environmental, metabolic, and lifestyle risk factors.[1] Exploring effective interventions is a key issue in the treatment of ND. Although a variety of drugs have shown potential therapeutic effects in ND, many challenges arise when applying these drugs in the treatment of ND. The pathological characteristics of different ND vary considerably due to the inconsistency of their focal sites. On the other hand, the solubility, stability, pharmacokinetic and toxicity profiles, physicochemical properties,

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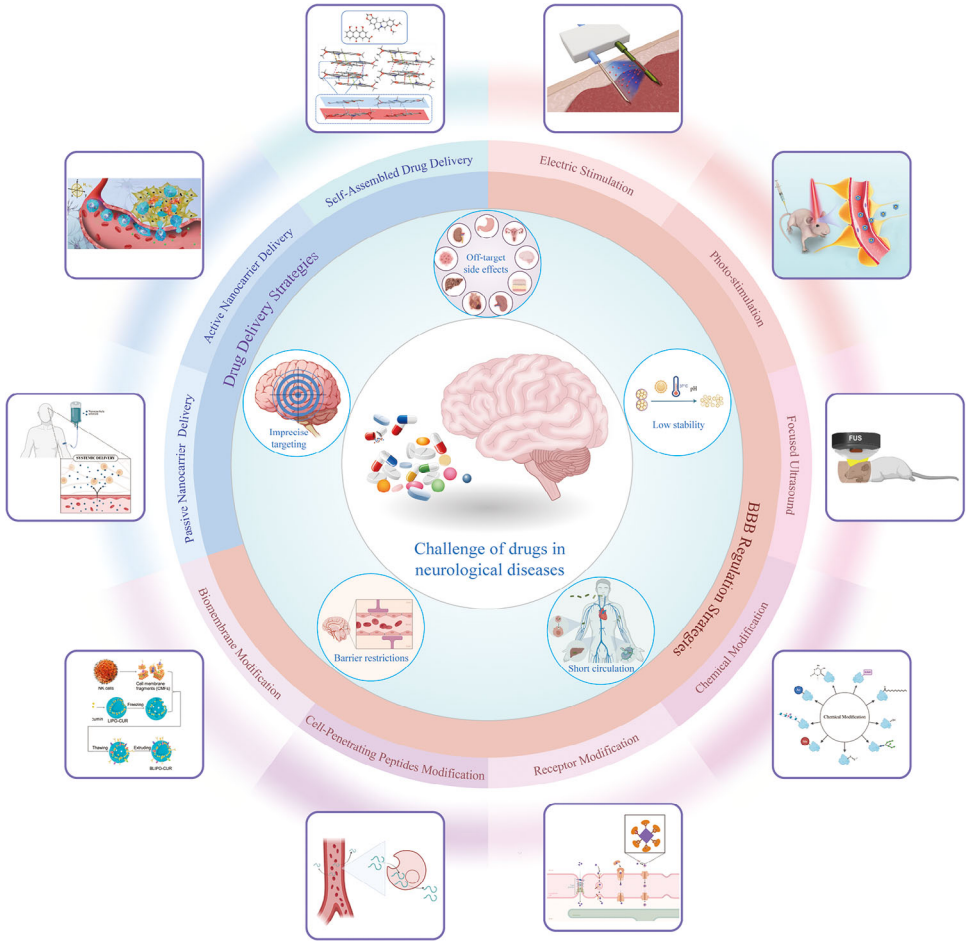

Figure 1. Schematic illustration of major contents in this review.

metabolism, and in vivo distribution of the drugs vary greatly when they enter the human body.[2] This makes some drugs face various problems, including poor bioavailability and biological stability, challenges in crossing biological barriers, the blood-brain barrier (BBB), significant off-target effects, substantial side effects, a short half-life in vivo, and a high clearance rate, in the process of entering the human body to reach the central nervous system (CNS) foci, which makes the drugs unsatisfactory for the treatment of ND.[3] For example, some drugs utilized orally face adverse gastrointestinal reactions, especially these radiotherapy drugs applied to brain tumor and anticoagulants used in the prevention of cerebrovascular disease.[4,5] In addition, different ND have specific sites of onset. Ischemic stroke occurs mainly in the middle cerebral artery, anterior cerebral artery, and posterior cerebral artery infarction.[6] In contrast, intracerebral hemorrhage (ICH) is prevalent in the basal ganglia.[7] Therefore, drugs entering the body face the problem of poor targeting in the affected areas of these foci. Finally, most drugs face a common barrier to entry into the CNS – the BBB. The BBB prevents many drugs from reaching the CNS.[8] In order for drugs to better fulfill their therapeutic role in ND, there is a need for targeted drug delivery strategies for different drugs to treat different ND.

In the last two decades, a wide variety of drug delivery strategies have emerged in response to technological advances to address the various problems faced in getting drugs into the body.[9,10] These strategies play an important role in addressing the challenges faced by specific drug delivery, thereby increasing drug efficacy, reducing side effects, and improving the therapeutic experience for patients. In this review, we detail the challenges faced by drugs entering the human body and summarize the various existing BBB regulation strategies and drug delivery strategies (**Figure 1**). Finally, the applications of the various delivery strategies in major ND are described.

2. Challenges in Pharmacological Treatment of Various Neurological Disorders

The CNS faces great challenges in clinical drug development due to its special physiological configuration. The main reason for this is the limitation of physiological barriers such as the BBB, which prevents various molecules from entering the CNS.[11] In addition, most CNS diseases have complex pathological mechanisms, making it difficult to precisely target drugs. Another factor is that neurons in the CNS system are highly susceptible to external factors, and external drug interventions are likely to produce non-targeted interventions on neurons in normal areas. Problems faced in the treatment of neurological diseases from oral drugs to intravenous drug delivery include the following:

off-target side effects (gastrointestinal reactions, organ toxicity), low stability, short circulation half-life (immunological clearance, enzymatic degradation, organ metabolic clearance), barrier restrictions, and imprecise targeting (**Figure 2**).

2.1. Neurological Treatment-Specific Off-Target Side Effects

2.1.1. Gastrointestinal Reactions in Neuropharmacology

The unique pharmacokinetic requirements of neurological drugs create paradoxical challenges. While oral administration facilitates chronic treatment compliance for neurological diseases, it simultaneously exposes vulnerable gastrointestinal tissues to neuroactive compounds. Some drugs used in ND that pass through the gastrointestinal tissues cause irritation of the gastrointestinal mucosa, resulting in gastrointestinal side effects. For example, the chemotherapeutic drug temozolomide (TMZ), which is used in the treatment of brain tumors, causes direct damage to the mucosa of the gastrointestinal tract. Routine oral use of these chemotherapeutic agents produces gastrointestinal reactions including lack of appetite, nausea, vomiting, poor appetite, nausea, vomiting, and diarrhea.[12] In addition, long-term use of levodopa for the treatment of PD can lead to nausea, vomiting, loss of appetite, and constipation.[13] Similarly, after taking Alzheimer's drugs such as donepezil, memantine, and mannequin, corresponding side effects have occurred, including diarrhea, nausea, vomiting, loss of appetite, and fatigue.[14,15] In the secondary prevention of ischemic stroke, long-term use of aspirin may lead to gastric mucosal damage, causing gastric mucosal erosion, ulcers, and even gastric bleeding.[16,17]

2.1.2. Neuropharmacology-Driven Organ Toxicity

Neuropharmacology-driven organ toxicity is a significant concern in both clinical and research settings, as it involves the adverse effects of neuropharmacological agents on organ functions. For example, some neuropharmacological agents may interfere with neurotransmitter systems, which can disrupt normal physiological functions in organs such as the liver, kidneys, and heart. After entering the body, neuropharmacological agents are distributed throughout the bloodstream. The kidneys and the liver are the two most important sites of blood filtration and removal, and with a combined blood flow of more than 45% of cardiac output, the kidneys and the liver are the most important organs for receiving molecular drugs.[18,19] One of the primary concerns with neuropharmacological agents is their potential to induce hepatotoxicity, which can lead to acute liver failure. This is particularly relevant for psychotropic medications, which are known to have hepatotoxic potential. For instance, drugs like nefazodone, pemoline, and tacrine have been identified as high-risk offenders for inducing liver damage, especially in patients with preexisting liver conditions or those at risk of liver injury.[20–22] Besides, triptolide is helpful in the treatment of cognitive disorders, but taking tretinoin produces significant liver and kidney toxicity.[23,24] Atorvastatin is a drug used to control hyperlipidemia and is used clinically for the prevention of cerebrovascular disease.[25] However, the use of atorvastatin produces hepatic metabolic toxicity in some populations.[26] Phenytoin sodium (PHT) is one of the most commonly used drugs for the treatment of generalized tonic-clonic seizures and status epilepticus.[27] PHT is mainly metabolized by the liver, and chronic mild elevation of liver enzymes is relatively common in long-term PHT therapy.[28] In addition to hepatotoxicity, neuropharmacological agents can also cause nephrotoxicity, leading to kidney damage. The mechanisms underlying drug-induced nephrotoxicity often involve oxidative stress and inflammation. For example, acetaminophen, a common analgesic, can cause hepatorenal toxicity, with sex and hormonal differences influencing the extent of damage.[29]

2.2. Low Stability of Neuropharmacological Agents

The stability of CNS drugs is a critical factor in their efficacy and safety. Stability issues lead to reduced therapeutic effects and increased risk of side effects, which is particularly concerning for CNS drugs due to their complex mechanisms of action and the delicate nature of the brain environment. The stability of these drugs can be influenced by various factors, including their solubility and metabolic activity.

Instability of therapeutic agents poses universal challenges in drug delivery, especially within heightened complexity in neurological contexts due to the unique neurophysiological microenvironment. First, the BBB imposes stringent structural constraints. While peripheral drugs may tolerate modest molecular modifications, neurological agents must maintain precise stereochemical configurations to facilitate receptor binding and BBB penetration through specific transport mechanisms. For instance, L-Dopa's chiral structure proves indispensable for its dopamine-replacement efficacy in PD, yet renders it susceptible to premature racemization in systemic circulation.[30] Second, CNS-specific microenvironment accelerates drug inactivation. Cerebral endothelial cells exhibit a 3-fold higher expression of monoamine oxidase compared to peripheral tissues, dramatically reducing the therapeutic window for neurotransmitters and their analogs.[31] This enzymatic barrier notably compromises the efficacy of serotonin-norepinephrine reuptake inhibitors in depression treatment.[32] Third, some neuropharmacological agents are photosensitive in common environmental conditions, making them vulnerable to processes such as oxidation, or isomerization. The delicate redox balance within neural circuits makes them exceptionally vulnerable to oxidative byproducts from drug degradation. For example, Anthocyanins, which are found in plant cells throughout nature, are water-soluble natural plant pigments with strong human bioactivities, such as anti-inflammatory and antioxidant properties. Anthocyanins' antioxidant potential in Alzheimer's models, while promising, is undermined by their rapid isomerization in cerebrospinal fluid (CSF) – a phenomenon distinct from their instability in peripheral circulation.[33,34]

2.3. Short Circulation Half-Life

2.3.1. Immunological Clearance

The immunological clearance of CNS drugs is a complex process that involves the coordinated actions of various immune

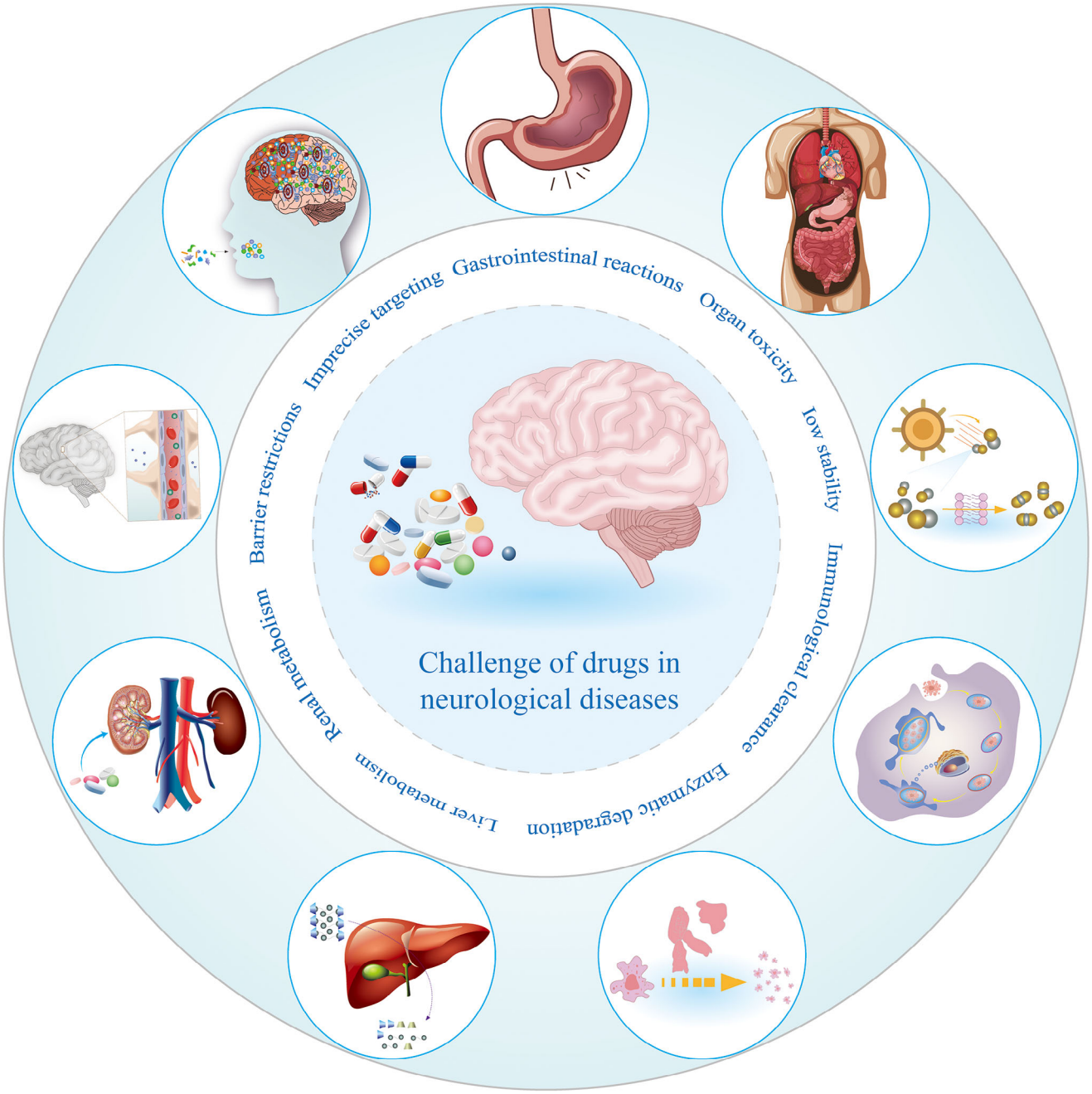

Figure 2. Various challenges in drug entry into the central nervous system.

cell types in the choroid plexus (ChP) and blood vessels, including macrophages, microglia, and brain-adapted monocyte populations. The monocyte-macrophage system is capable of the uptake of a wide range of drugs, including small molecule drugs and larger biomolecules, mediated by cell surface receptors such as Fc receptors and oligonucleotide receptors. In addition, another of the critical components in this process is the role of microglia, the resident immune cells of the CNS. Microglia are known to respond to various conditions, including the presence of foreign substances such as drugs, by initiating an immune response that can lead to the clearance of these substances from the CNS.[35]

ChP plays a critical role in the CNS by acting as a barrier and a clearance mechanism for various substances, including drugs. The macrophages residing in the ChP are particularly significant in this process. These immune cells are involved in the uptake and clearance of CSF-circulating drugs, utilizing mechanisms such as Toll-like receptor 4 (TLR4)-mediated pathways.[36,37] The ChP's role in drug removal is supported by its expression of various transporters and enzymes that facilitate the efflux of

xenobiotics and metabolites from the brain into the blood, thus maintaining the brain's functional integrity. The ChP macrophages, through TLR4-mediated uptake, can filter a significant percentage of drugs from the CSF.[38] In conclusion, the choroid plexus, through its macrophages and other cellular components, plays a vital role in the clearance of CSF-circulating drugs and the regulation of immune responses in the CNS. Understanding these mechanisms provides insights into potential therapeutic strategies for managing CNS disorders and enhancing drug delivery to the brain.

Another key mechanism involved in CNS drug clearance is the trapping of drugs by perivascular macrophages. These macrophages are strategically located around blood vessels, allowing them to interact closely with the vascular system and respond to changes in the local environment. Recent studies have shown that more than 80% of administered edaravone, a neuroprotective agent used in the treatment of conditions such as amyotrophic lateral sclerosis (ALS), accumulates in these perivascular macrophages.[39] This accumulation is significant as it highlights the role of macrophages in the sequestration and clearance of drugs from the CNS. The mechanism of drug trapping by perivascular macrophages is somewhat analogous to the process described in brain endothelial cells, where lysosomal sequestration and subsequent disposal by neutrophils play a crucial role.[40] In the context of the BBB, endothelial cells express high levels of active efflux transporters, such as P-glycoprotein (Pgp), which are involved in the extrusion of drugs from the brain. Pgp not only actively transports drugs out of the cells but also mediates their lysosomal sequestration, contributing to drug resistance in cancer cells. This process is followed by the shedding of drug-sequestering vesicular structures, which are eventually phagocytosed by neutrophils, thus facilitating drug disposal.[41]

2.3.2. Enzymatic Degradation

The short circulation half-life of drugs targeting the CNS is a significant challenge in therapeutic development. One of the primary reasons for this limited half-life is the enzymatic degradation that these drugs undergo once administered. Enzymes present in the bloodstream and tissues can rapidly break down therapeutic agents, reducing their effective concentration and duration of action. This enzymatic activity necessitates frequent dosing, which can be inconvenient for patients and may lead to increased side effects. The enzymatic degradation of CNS drugs involves various enzymes, including cytochrome P450s, esterases, and hydrolases, which facilitate the breakdown of drug molecules into metabolites that can be more easily excreted from the body. Especially, the cytochrome P450 enzyme family, as a membrane-bound hemoglobin, is the main enzyme involved in drug metabolism in the body and plays an important role in drug detoxification, cellular metabolism, and homeostasis. It is involved in ≈75% of drug metabolism reactions.[42,43] When being absorbed by the body, CNS drugs undergo chemical structural transformation under the action of these enzymes and are subsequently degraded.[44] The drug is rapidly inactivated by enzymatic degradation in serum, resulting in a very short half-life, which seriously hampers its clinical application in ND.[45]

2.3.3. Organ Metabolic Clearance

The short circulation half-life of CNS drugs is a significant challenge in pharmacotherapy, primarily due to the metabolic clearance by major organs such as the liver and kidneys. The liver, being the primary site for drug metabolism, utilizes various enzymes to transform drugs into more water-soluble metabolites, facilitating their excretion. The liver contains a large number of uptake/excretion transporters and abundant drug-metabolizing enzymes.[46] After entering the hepatocyte by passive diffusion or active uptake, drug molecules are cleared by metabolic reactions catalyzed by different metabolic enzymes. There are also drugs that are not metabolized and are cleared directly in the form of prototypes through biliary excretion. This process often leads to a rapid decrease in the active concentration of the drug in the bloodstream, thereby shortening its half-life and potentially reducing its therapeutic efficacy. Similarly, the kidneys play a crucial role in drug clearance through filtration and excretion of metabolites in the urine. Renal excretion consists of three main processes, namely glomerular filtration, active tubular secretion, and tubular reabsorption.[47] Free small molecules that are not bound to plasma proteins enter the proximal renal tubule via glomerular filtration.[48,49] The more lipid-soluble molecules, which are readily reabsorbed in the tubules back into the circulation, are usually excreted as polar metabolites after metabolic transformation in phase I and phase II.[50] The efficiency of these organs in metabolizing and excreting drugs can significantly influence the pharmacokinetics and pharmacodynamics of CNS drugs, necessitating careful consideration in drug design and dosing regimens.

2.4. Barrier Restrictions

The BBB is a selective barrier in the CNS consisting of capillary endothelial cells, basement membranes, pericytes embedded in these membranes, and astrocytes.[51] The BBB is characterized by a high transendothelial electrical resistance and a low paracellular and transcellular permeability, which ensures a high degree of selectivity in the exchange of substances between the brain and the external environment, thus limiting the entry of small molecule drugs and toxic substances.[52,53] Due to the presence of the BBB, the treatment of CNS diseases is difficult. Almost 100% of large-molecule drugs and ≈98% of small-molecule drugs currently used in clinical practice have difficulty crossing the BBB to enter the CNS.[54,55]

2.5. Imprecise Targeting

The challenge of achieving precise targeting of drugs within the CNS is a significant hurdle in the treatment of ND. The complexity of the CNS, coupled with the presence of protective barriers, complicates the delivery of therapeutic agents to specific sites within the brain and spinal cord. Notably, Most ND exhibit distinct neuroanatomical tropism, but the non-specific targeting of drugs often causes adverse reactions in the CNS, especially to healthy tissues. Neurodegenerative diseases, such as AD and PD, involve several different brain regions and are usually characterized by neurodegeneration in specific areas. The main sites of AD

are the frontal lobe, temporal lobe, and hippocampus, especially the hippocampus, which is characterized by neuroinflammatory plaques, neuroprogenitor fiber tangles, neuronal loss, and amyloid angiopathy.[56,57] PD, on the other hand, mainly affects landmark areas such as the basal ganglia and substantia nigra, resulting in impaired motor coordination and cognitive function.[58] ALS affects the spinal cord and primary motor cortex, resulting in severely impaired voluntary muscle control and certain executive functions.[59] Meanwhile, multiple sclerosis is characterized by focal demyelinating lesions in the white and grey matter of the CNS.[60] Current pharmacopeia for these conditions, including levodopa for PD and edaravone for ALS, remain fundamentally limited by inadequate target specificity. This therapeutic imprecision becomes particularly problematic given the emerging understanding of region- and cell-type-specific vulnerabilities in CNS disorders. The hippocampus' metabolic peculiarities in AD, the substantia nigra's unique iron homeostasis in PD, and spinal motor neurons' distinct electrophysiological properties in ALS all underscore the necessity for advanced delivery systems capable of spatial and cellular resolution. Since brain regions differ in their susceptibility to various neuropathies, there is an urgent need to target specific regions for drug delivery to the brain.

The numerous challenges in neurological drug delivery including off-target effects, stability issues, rapid clearance, BBB restrictions, and imprecise targeting collectively underscore the urgent need for advanced delivery strategies. These limitations of conventional approaches directly motivate the development of innovative solutions discussed. By addressing pharmacokinetic shortcomings while overcoming biological barriers, next-generation delivery systems can achieve targeted CNS drug accumulation with reduced systemic exposure. The following section systematically examines these emerging strategies, from physical stimulation to nanocarriers, each designed to circumvent specific delivery challenges.

3. BBB Regulation Strategies

3.1. BBB Regulation Based on Physical Stimulation

Drug delivery in the nervous system is a complex and challenging area, primarily involving the delivery of drugs to the brain through the BBB. Physical stimulation has received much attention as a way to modulate the BBB. Physical methods such as photo-stimulation and electrical stimulation are used to temporarily disrupt the BBB, opening it up and increasing drug permeability.

3.1.1. Electric Stimulation

Electroporation is a technique in which the cell membrane is electrically stimulated by the application of a high-intensity electric field sufficiently to promote the formation of micropores, and allow various molecules to pass through the membrane, has been used for BBB regulation. Electroporation increases the permeability of the cell membrane by means of electrical impulses, creating pores in the cell membrane that can enable the transport of foreign substances into the intracellular environment.[61] For example, to assist drug delivery to deep tissues, Lee et al. designed a nanopore-electroporation system with a two-needle array electrode consisting of a metal needle and a nanopore needle electrode with a drug release zone on the side for drug delivery to deep tissues in the body.[62] This nanopore electrode effectively focuses the electric field, which can only act on the cells surrounding the nanopore. The platform is based on nanopore needle electrodes fabricated through a fusion of micron and nanofabrication technologies, which feature low tissue damage and high transfection efficiency (**Figure 3a**). Fang et al. explored the clinical translation of electroporation for brain tumors. The effect of electroporation-based therapy on brain tumors was summarized, and electroporation-induced transient disruption of the BBB may improve the absorption of anti-tumor drugs.[63] Electroporation, as a non-invasive drug delivery system, is an effective method for drugs to breach the BBB. By utilizing a brief electric field action, electroporation can open specific channels in the BBB, thus allowing drugs to enter the CNS more rapidly, thus acting as a therapeutic agent for ND. It can be used to assist nanocarriers in delivering drugs to the CNS for the treatment of ND.

3.1.2. Photo-Stimulation

Under near-infrared laser irradiation, its photothermal effect can increase the permeability of the BBB and promote the entry of drugs into the CNS. For instance, Liu et al. synthesized a zeolite imidazolium backbone 8-coated Prussian blue nanocomposite (ZIF-8@PB) encapsulated with quercetin (QCT) for the treatment of PD. ZIF-8@PB-QCT exhibited an excellent response to near-infrared radiation (NIR) and was guided by photothermal effects across the BBB to reach the site of mitochondrial damage (Figure 3b). Used in a mouse model of PD, ZIF-8@PB-QCT significantly increased adenosine triphosphate levels, decreased oxidative stress levels, and reversed dopaminergic neuronal damage as well as PD-associated behavioral deficits without any damage to normal tissues.[64] In another study, Yin et al. design of a core/shell structure triggered by NIR light of two dimethyl (2D) silicone nanosheets coated with a mesoporous silica layer has been rationally constructed as a topical drug delivery system in sciatic nerve bloc.[65] Based on the specific photothermal properties of the 2D silica core, this local anesthesia system can be triggered by a near-infrared laser to release loaded RP for on-demand and long-lasting regional anesthesia. NIR-responsive nano drugs can non-invasively control the drug delivery process spatially and temporally without affecting healthy tissues, and their photothermal effect in the presence of NIR stimulants enhances the permeability of the BBB, thus they have a high potential for drug delivery in ND.

3.1.3. Focused Ultrasound

Focused ultrasound (FUS) has emerged as a promising technique for opening the BBB to facilitate drug delivery to the CNS. When combined with microbubbles, FUS offers a non-invasive method to transiently and locally disrupt the BBB, thereby enhancing the delivery of drugs to targeted brain regions.[66,67] The use of FUS for BBB opening has been extensively studied in preclinical models, demonstrating its potential to improve

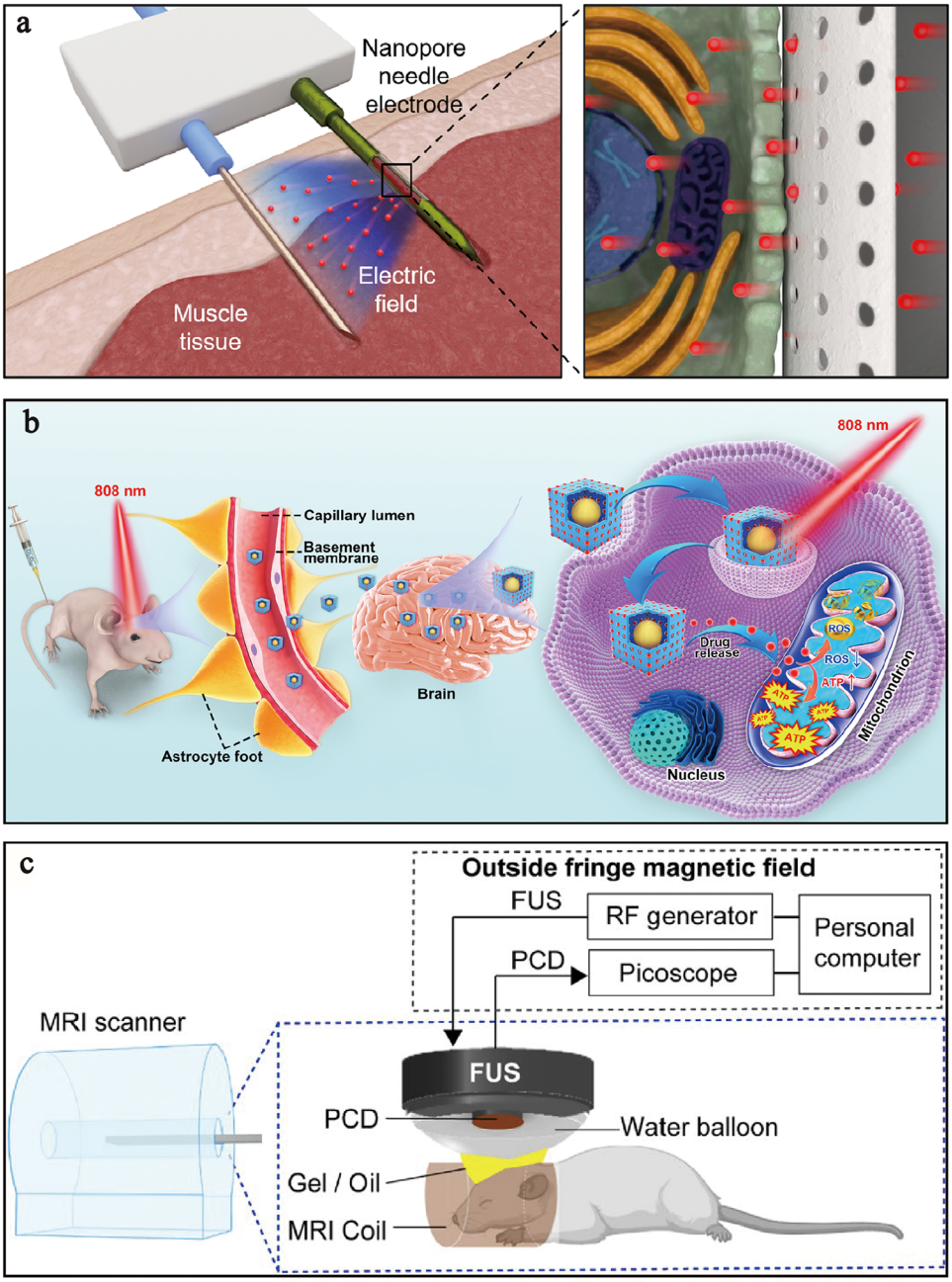

Figure 3. Representative strategies of physical stimulation on BBB regulation. a) Schematic illustration of the in vivo nanopore-electroporation system. That consists of a conventional metal needle and nanopore needle electrode with a side drug-releasing compartment. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [62]. Copyright 2022 Gyeong Won Lee et al., published by Wiley Periodicals LLC on behalf of the American Institute of Chemical Engineers. Bioengineering & Translational Medicine published by Wiley Periodicals LLC. b) Schematic illustration of photo-stimulation opening the BBB. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [64]. Copyright 2021 Yao Liu et al., published by American Chemical Society. c) Schematic illustration of a Focused Ultrasound (FUS) system. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [70]. Copyright 2023 Lu Xu et al., published by Springer Nature.

drug delivery for various CNS diseases, including brain tumors, AD, and PD. The technique involves the application of focused acoustic energy to specific brain areas, which, in the presence of microbubbles, causes a temporary increase in BBB permeability. This allows therapeutic agents that are otherwise unable to cross the BBB to reach the brain tissue.[68] Magnetic resonance imaging (MRI) guidance is often used to precisely target the ultrasound to specific brain regions, ensuring that the BBB opening is localized and minimizing potential side effects. Additionally, real-time monitoring of acoustic emissions during FUS

treatment helps in optimizing the parameters for safe and effective BBB disruption.[69] Transcranial FUS-induced opening of the BBB in mice can be achieved without shaving the hair by using an oil fluid as a coupling medium (Figure 3c).[70] Xue et al. fabricated a system of ultrasound-responsive nanobubbles (NBs) to load the asparagine endopeptidase (AEP) inhibitor RR-11a for targeted intracerebral delivery of AEP inhibitors.[71] They prepared ultrasound-responsive NBs loaded with RR-11a and modified the surface of the NBs with an RGD peptide to promote the opening of the BBB during FUS oscillations, and the surface of the NBs was modified with an AAN peptide to increase the binding of the NBs to the neuronal binding. Enhancing the instantaneous opening of the BBB during FUS oscillations allowed the remaining NBs and locally released RR-11a molecules to enter the brain, and NB (11a)-A could selectively bind to damaged neurons and deposit RR-11a molecules at AD lesions. The results suggest that this synergistic nanobubble delivery system provides an effective method to improve the BBB of damaged neurons, increase drug accumulation at AD lesions, and effectively improve therapeutic efficacy.

3.2. Modification of Nanocarriers for BBB Modulation

Drug-carrying nanoparticles synthesized in vitro and injected intravenously face complex BBB challenges. The special microenvironment of the nervous system makes it difficult for nanoparticles to penetrate the BBB and precisely release drugs at the lesion site. To break through these limitations, surface modification technology has become a key strategy to regulate the targeting and biocompatibility of nanocarriers. Through chemical or receptor-mediated modifications, antibodies, aptamers, peptide ligands, or small molecules can be grafted on the surface of nanoparticles to specifically recognize BBB endothelial cell surface markers (e.g., transferrin receptor or low-density lipoprotein receptor), thereby enhancing cross-barrier ability and lesion enrichment. In addition, cell-penetrating peptide modifications promote active transmembrane transport of the carrier, while biofilm-mediated modifications (e.g., biomimetic membrane coating) significantly reduce immunogenicity and prolong in vivo circulation time. These functionalized modification strategies not only optimize the targeted delivery efficiency of the nanocarriers but also provide a new direction for regulating BBB permeability and achieving precise neurotherapy.

3.2.1. Chemical Modification

Chemical modification strategies such as polyethylene glycolysis (PEGylation), polysialic acidylation (PSAylation), and esterification (Lipidation) are considered to be some of the most effective methods for controlling the in vivo clearance of drugs due to their structures, low impurities, and proven methods.[72,73] The key to chemical modification strategies is to maximize the half-life without compromising the biological activity of the drug, which requires a comprehensive understanding of the structure-activity relationship of the drug as well as precise site modification methods. To address the challenge of low brain concentration and bioavailability of Goutenine and improve the precision of brain targeting, Xu et al.[74] synthesized methoxy polyethylene glycol polylactic-co-glycolic acid (mPEG-PLGA) nanoparticles loaded with willow leaf alkaloid (NPS-RIN), and further modified with T80 for targeted brain delivery (T80-NPS-RIN). T80-NPS-RIN facilitated RIN's entry into the brain via the BBB and modulate neuronal activity, offering neuroprotection in AD mice. An ultrasound-triggered nano-delivery system that can stably encapsulate Astaxanthin (ATX) has been designed and established by Wei Cai and his group.[75] The core of the system is a perfluorocarbon (PFH) droplet loaded with ATX and IR780. The outer layer is a polydopamine (PDA) hard shell. When triggered by ultrasound, the PFH changes from liquid to gas and releases ATX, while the PDA protects the ATX from light. The PDA protects the ATX from light exposure. After the nanoparticles pass through the BBB, the ATX is released under ultrasound, which enhances the therapeutic efficacy of the ATX.

3.2.2. Receptor Modification

Receptor-mediated transport (RMT) is a promising strategy for drug delivery across the BBB. RMT utilizes the natural transport mechanisms of the BBB by exploiting specific receptors that facilitate the transcytosis of molecules from the bloodstream into the brain parenchyma. This approach has gained considerable attention due to its potential to enhance the delivery of therapeutic agents to the CNS.[76] One of the key advantages of RMT is its ability to transport macromolecules, such as antibodies, peptides, and proteins, across the BBB. These macromolecules can be conjugated with ligands that have a high affinity for specific receptors on the endothelial cells of the BBB, such as the transferrin receptor or the insulin receptor. Upon binding, the ligand-drug conjugate is internalized via endocytosis and transported across the endothelial cells to be released into the brain tissue. This method has been shown to improve the delivery of therapeutic agents for various brain diseases, including AD and PD.[77] Recent advancements in RMT strategies have focused on optimizing the design of drug carriers and ligands to enhance their specificity and efficiency. For instance, drug carriers have been functionalized using targeted ligands to facilitate receptor-mediated endocytosis and translocation across the BBB.[78,79]

3.2.3. Cell-Penetrating Peptides Modification

Cell-penetrating peptides (CPPs) have emerged as a promising tool for drug delivery, particularly in overcoming the challenges posed by the BBB in the CNS. CPPs, with their ability to traverse cellular membranes, offer a potential solution to the BBB by facilitating the delivery of bioactive molecules into the brain.[80] One of the primary advantages of CPPs is their ability to transport a wide range of therapeutic agents, including proteins, nucleic acids, and small molecules, across the BBB, which is crucial for the treatment of CNS-related diseases. Despite their potential, the clinical application of CPPs has been limited by issues such as non-specificity and potential toxicity. However, recent advances

in the design of CPPs, including the development of novel CPP-mediated nanoparticulate delivery systems with specific targeting properties, hold promise for overcoming these challenges.[81,82] The use of CPPs in conjunction with other drug delivery technologies, such as liposomes and nanoparticles, has shown significant promise in enhancing the delivery efficiency and therapeutic efficacy of drugs targeting the CNS. For instance, CPP-coated liposomes have been developed to improve the delivery of drugs like doxorubicin to glioma cells, a deadly form of brain cancer. These CPP-modified liposomes have demonstrated improved cellular uptake and increased drug accumulation in the brain, highlighting their potential as effective delivery vehicles for CNS-targeted therapies.[83]

3.2.4. Biomembrane Modification

Using cells in vivo to design cell membrane-based biomimetic nanoparticles, this method of integrating natural cell membranes onto the surface of nanoparticles can incorporate various advantages of molecular proteins on the surface of cell membranes and the chemical properties of membrane materials into one, endowing the biomimetic nanocarriers with good biocompatibility, thus escaping clearance by the immune system and decreasing immunogenicity. It also prolongs the circulation time of nanoparticles in the blood system. In addition, cell membranes originating from organisms have the ability to homologously target different foci, which greatly enhances the enrichment of nanoparticles at the site of the lesion, thus increasing the therapeutic efficiency and reducing toxic side effects.[84] Biomimetic membrane materials have been developed and applied to ND that can address the above-mentioned limitations and shortcomings of nanomaterials. Common biomimetic membrane nanomaterials include erythrocyte membrane, platelet membrane, neutrocyte membrane, macrophage membrane, mesenchymal dry membrane and cancer cell membrane. In a recent study, Jinlian Gu and her group developed a red blood cell (RBC) membrane-coated polycaprolactone (PCL) nanoparticle loaded with curcumin (Cur) for the treatment of AD (**Figure 4a**).[85] The functional peptide TGNYKALHPHN (TGN) was coupled to the membrane surface (TGN-RBC-NPS-CUR) for BBB transport. The complete red blood cell membrane is covered on the surface of the nanoparticles, giving the physical and chemical properties of the red blood cell nanoparticle synthesis material and the complex biological functions of the endogenous material. Compared to nanocarriers based on synthetic materials, RBC NPs have a larger cycle half-life and show low immunogenicity. In another study, Liu et al. created a natural killer cell membrane mimetic nanocomplex (named BLIPO-CUR) delivered via the meningeal lymphatic vessel (MLV) pathway to further enhance the therapeutic effect of PD (Figure 4b).[86] The membrane binding enables BLIPO-CUR to target damaged neurons, inhibit the aggregation of α-synuclein by scavenging ROS, and inhibit the diffusion of excess α-synuclein, thus improving its therapeutic efficacy. Su et al. established a transferritin receptor aptamer-modified erythrocyte membrane camouflaged nanomedical drug delivery system (TR-ZRA) that can be targeted across the BBB to improve the AD immune environment (Figure 4c).[87] Based on the metal-organic skeleton, TR-ZRA is loaded with CD22shRNA plasmid to silence the abnormally high expression of CD22 molecule in senescent microglia. Most importantly, TR-ZRA enhances the ability of microglia to phagocytose Aβ, easing complement activation, which promotes neuronal activity in the AD brain and reduces inflammation levels.

4. Drug Delivery Strategies

4.1. Nanocarrier-Based Drug Delivery

Nanocarriers play an important role in the drug delivery process. Nanocarrier-mediated drug delivery process is mainly through two delivery modes, passive and active. Each of these strategies has its own advantages and limitations, and the selection of an appropriate delivery strategy needs to be based on the nature of the specific drug, the therapeutic goal, and the patient's condition. In parallel with the development of new drugs, the development of effective delivery systems is essential to improve drug efficacy and minimize side effects.

4.1.1. Passive Delivery Strategies for Nanocarriers

Nanocarrier-based passive drug delivery processes limit drug therapeutic efficacy due to their insufficient targeting efficiency, poor release controllability, and off-target toxicity. By designing environment-responsive structures, the drug release efficiency and therapeutic controllability of passive delivery can be significantly enhanced.

ROS-Mediated Drug Release: Oxidative stress is a common pathological mechanism of many brain diseases including AD and PD. Oxidative stress produces excessive ROS, and a large accumulation of free radicals leads to abnormal cell signaling, which leads to the gradual degeneration of neurons. Constructing ROS-responsive drug delivery systems in local lesions has become an efficient and accurate intervention method. Nicotinamide adenine dinucleotide (NAD+) and Beclin1, which act as mitochondrial autophagy promoters, were rapidly released from P@NB in the presence of high ROS levels in the lesion to restore mitochondrial homeostasis and induce microglial cells to polarize toward the m2-type, which enables them to phagocytose Aβ. Yuan et al designed a ROS-responsive Ruthenium nanoplatform drug delivery system that promotes neuronal regeneration and Aβ clearance for the treatment of AD (**Figure 5a**).[88] When the nanoclusters effectively reach the brain, the higher ROS level in the lesion area will cause the -SE-SE-bond to break, and the diselenide bond in the nanoclusters will be destroyed, and the nanoclusters will be degraded into small ruthenium nanoparticles in the highly ROS environment in the lesion area, and the nerve growth factor will be released, effectively treating memory loss in AD mice. The construction of ROS-responsive drug delivery system can reduce the release in normal tissues and provide more focused intervention in local oxidative stress pathology. Mitochondrial autophagy modulation is considered as a potential therapeutic intervention for AD. However, the lack of specific mitochondrial autophagy inducers and the side effects of non-selective autophagy have limited their application. Yang et al. utilized P@NB nano-scavengers designed as reactive oxygen-responsive (ROS-responsive) poly (l-propylidene glycolide-hydroxyacetate) cores,

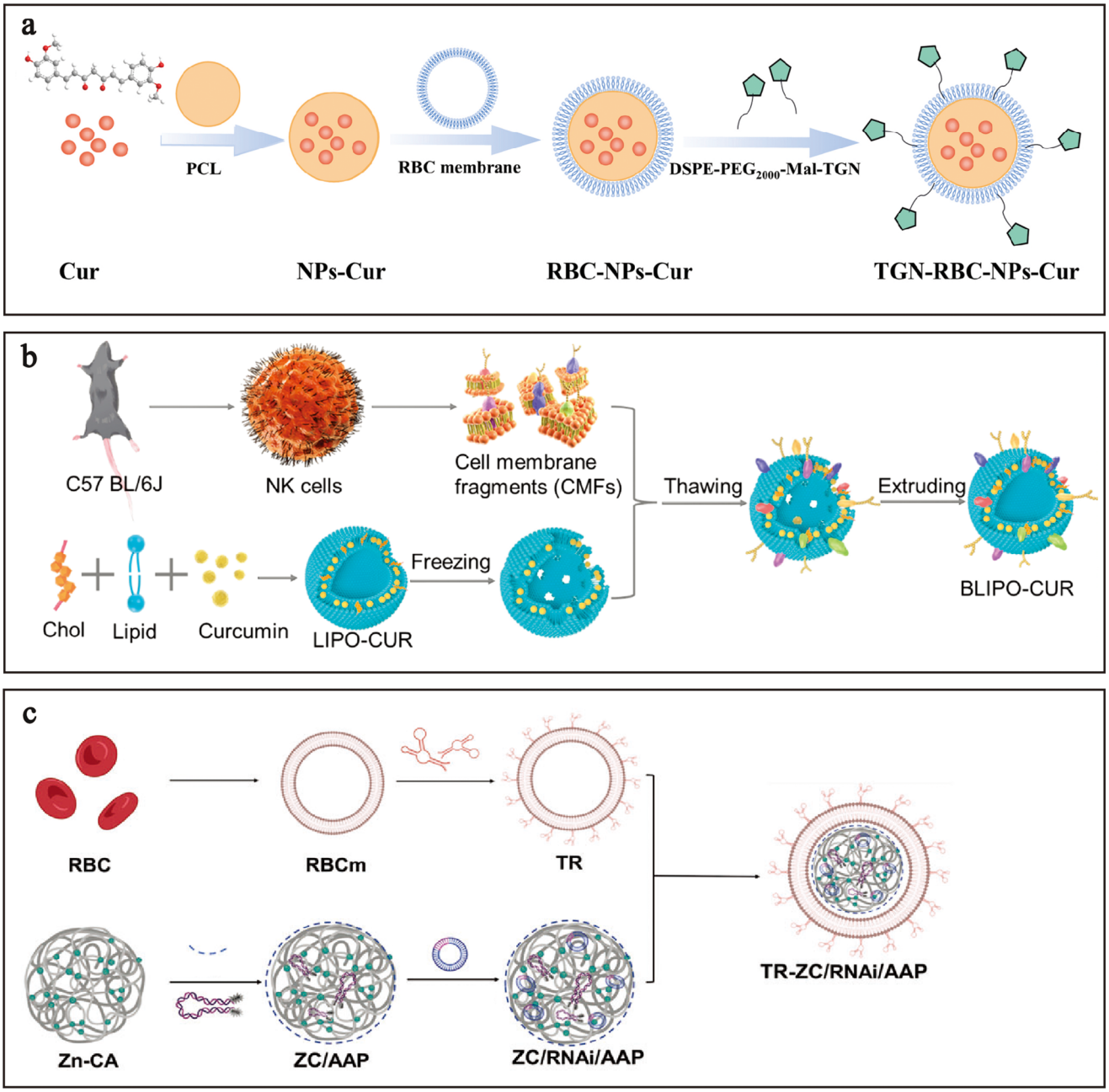

Figure 4. Representative drug-delivery strategies of Cell membrane-mediated modification. a) Schematic preparation of TGN-RBC-NPs-Cur. Reprinted with permission from ref. [85]. Copyright 2024 Elsevier B.V. b) Schematic illustration of the preparation of BLIPO-CUR. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [86]. Copyright 2023 Jing Liu et al., published by National Research Council. c) Schematic illustration of TR-ZC/RNAi/AAP preparation. Reprinted with permission from ref. [87]. Copyright 2023 The Authors and Wiley-VCH GmbH.

modified on the surface by Beclin1 and angiopoietin-2 peptides (Figure 5b).[89] In another study, Liu et al.[90] designed a modular nanoplatform consisting of a peptide-drug conjugate and an inflammatory response core. The nanoplatform could cross the BBB by transcytosis and introduced a ROS-sensitive cross-linker that decomposed in the oxidative stress microenvironment after intravenous injection (Figure 5c). The released drug-conjugated modules specifically target microglia and astrocytes to deliver hydroxychloroquine and all-trans retinoic acid, respectively. Moreover, Zhang et al. constructed nanocarriers named SPNPs with multiple functions such as mitochondrial targeting, ROS-responsive release, and anti-oxidative stress to achieve the treatment of ischemia/reperfusion injury by regulating the oxidative microenvironment and mitochondrial function (Figure 5d).[91] The thione cross-linking skeleton of the SPNPs would be fractured by microenvironmental ROS, which would play a role in eliminating the activity of ROS, and realize the controlled release of loaded puerarin. The abundance of ROS in

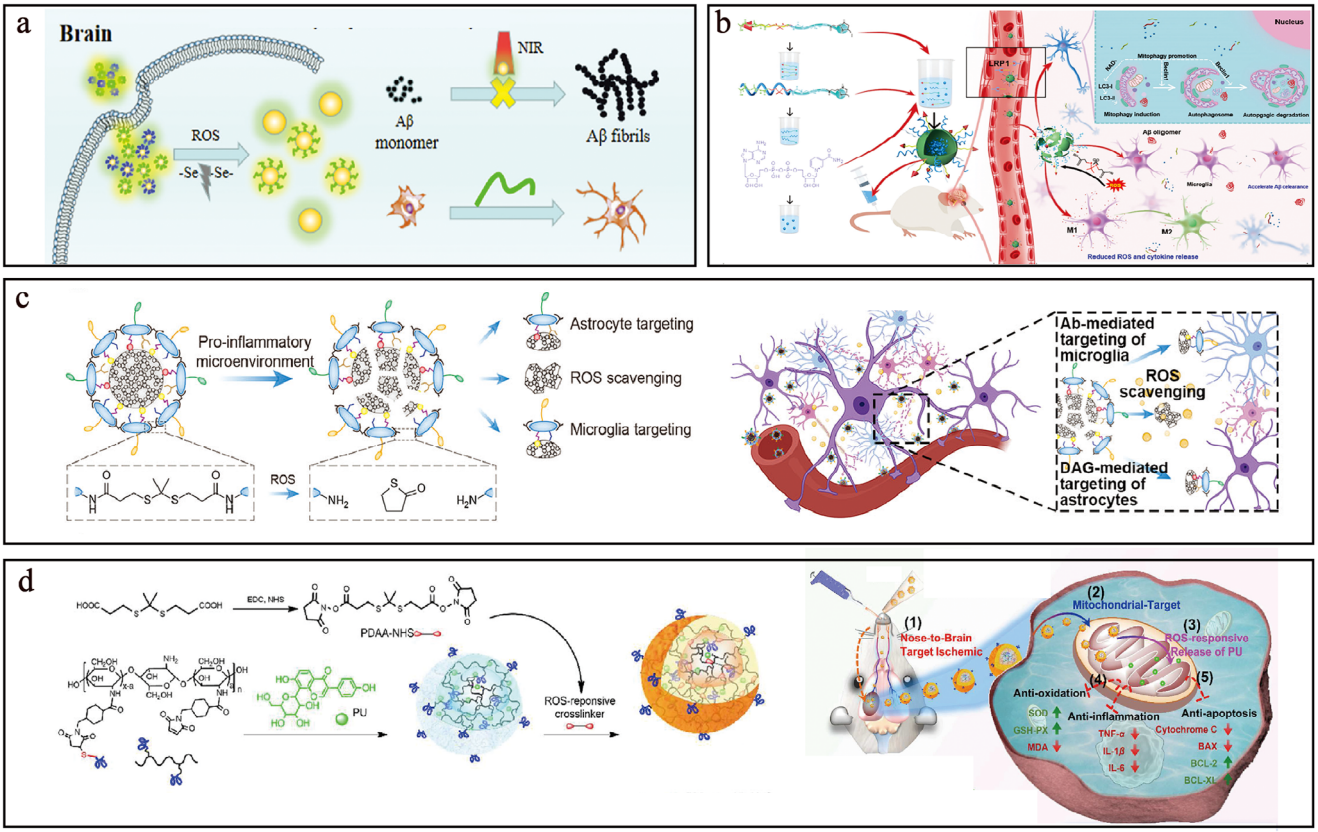

Figure 5. Representative ROS-responsive drug-delivery. a) Schematic illustration of the fabrication of the R@NGF–Se–Se–Ru nano-system and its uptake by the neuron cells. Reprinted with permission from ref. [88]. Copyright 2021 Royal Society of Chemistry. b) Schematic illustrating ROS-responsive P@NB that induces autophagy/mitophagy and improves cognitive functions in AD mice. Reprinted with permission from ref. [89]. Copyright 2023 Wiley-VCH GmbH. c) Self-assembly process of nanoplatform (DA-PPHATK@PDA). Reprinted with permission from ref. [90]. Copyright 2024 Wiley-VCH GmbH. d) Schematic illustration of targeted treatment of ischemic stroke by ROS-responsive nanoparticles loaded with PU and decorated with SS31. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [91]. Copyright 2022 Yan Zhang et al., and Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V.

mitochondria triggers the ROS-responsive skeleton in SPNPs and SS-31 to consume ROS, thereby reducing oxidative stress and inflammation.

pH-Mediated Drug Delivery: Another common endogenous response is the pH response. Some encephalopathic diseases such as AD, PD and stroke are characterized by microenvironments with pH imbalances at specific sites compared to normal tissues, and the development of a pH-responsive drug-releasing nano-delivery system that allows drugs to be appropriately released at therapeutically relevant concentrations has become an intervention strategy for individualized treatment regimens. The development of a pH-responsive "on-demand" drug delivery system has become an intervention strategy for individualized therapeutic regimens, whereby a nano-delivery system responsive to the diseased microenvironment can be disintegrated in response to a specific pH stimulus, thus enabling appropriate release of drugs in response to the pathology of the disease and minimizing non-specific accumulation of the drug. Cheng et al. designed a pH-sensitive rapamycin therapeutic nanoparticle system by taking advantage of the lower-than-normal pH of brain tissue in ischemic stroke (**Figure** 6a).[92] The nanoparticles have good stability and biocompatibility, can be effectively loaded with rapamycin, and are rapidly released in an acidic environment, thus improving the precision of treatment. In a separate study, in order to overcome the BBB and to achieve effective drug enrichment, Yang et al. develop a simple integrin ligand-conjugated, pH-responsive, dual-targeted nanoparticles (NPs) strategy for effective drug delivery to the ischemic brain (Figure 6b). It enables both pH-sensitive drug release and improved stroke efficacy by targeting cerebral ischemia. Due to the significant decrease in ambient pH in ischemic brain tissue, the reduced electrostatic adsorption capacity promotes the release of smooth agonists (SAGs) in acidic ischemic regions. In addition, delivery of SAG via pH-dependent electrostatic adsorption of PHSRN-HES strongly activates Shh signaling and promotes angiogenesis and neuroplasticity.[93] Similarly, Fan et al. developed neutrophil-camouflaged pH-responsive nanoparticles (G@NPEOz) that release therapeutic drugs in acidic environments with good biocompatibility and the ability to target sites of injury (Figure 6c).[94] G@NPEOz nanoparticles enhanced erythrocyte phagocytosis by inhibiting ADAM17-mediated shedding of exocytotic erythrocyte receptor MERTK/AXL and accelerating LXR-regulated ABCA-1/ABCG-1 mediated cholesterol efflux to enhance erythrocyte phagocytosis. It was found that one

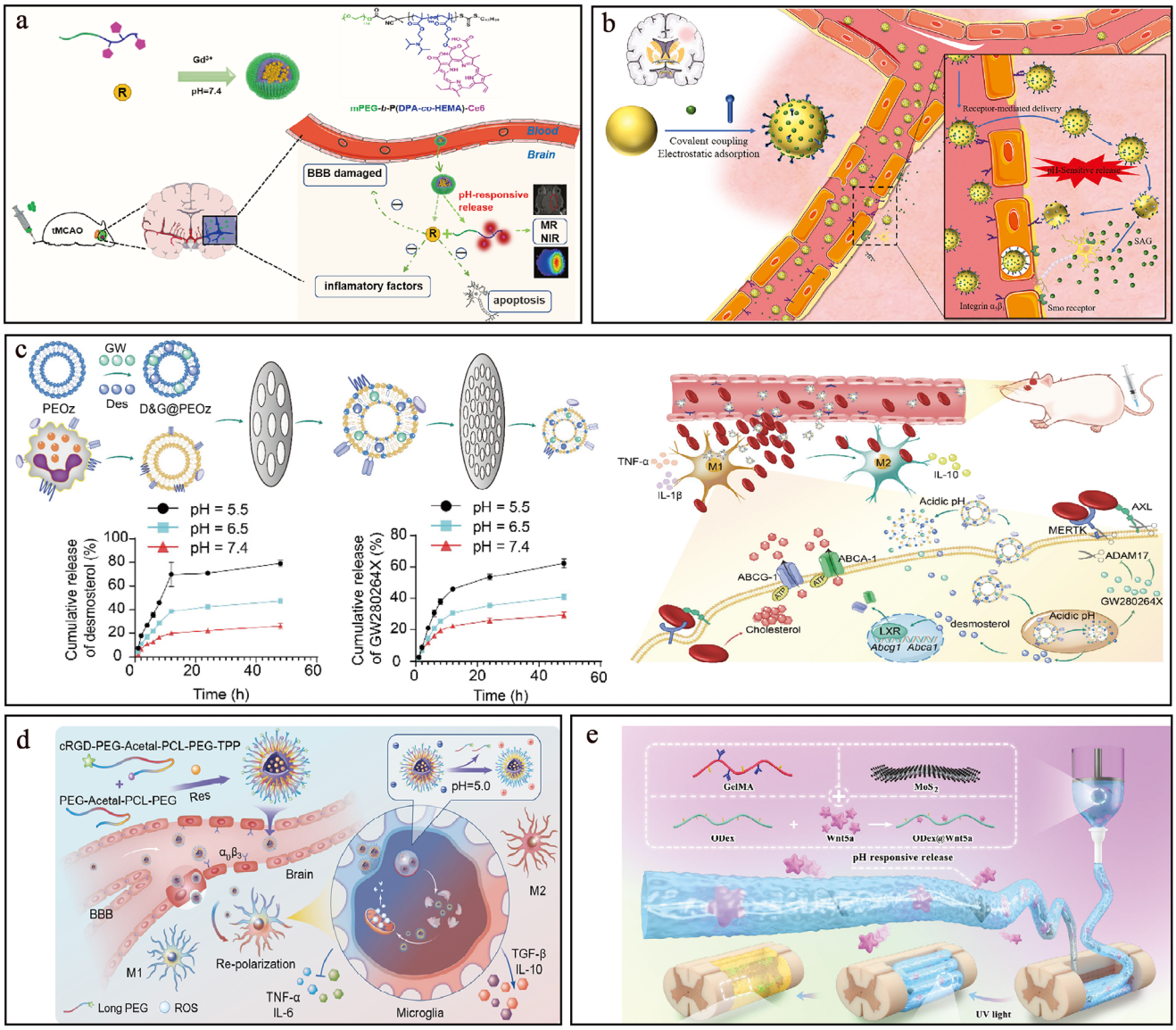

Figure 6. Representative pH-responsive drug-delivery. a) Schematic Illustration of the Preparation of theranostic nanoparticles (RAPA/Gd3+@NPs) and Their Preferential Accumulation in Cerebral Ischemic Lesions to Attenuate Ischemia/Reperfusion Injury during the Treatment of Ischemic Stroke. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [92]. Copyright 2021 Yan Cheng et al., published by American Chemical Society. b) Schematic illustration of the structure of SAG@PHSRN-HES and their application for active cerebral vasculature-targeting and pH-sensitive treatment of ischemic stroke. Reprinted with permission from ref. [93]. 2021 Wiley-VCH GmbH. c) Scheme of the D&G@NPEOz synthesis process and illustration of D&G@NPEOz therapy for erythrophagocytosis and neurological functional recovery after intracerebral hemorrhage (ICH). Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [94]. Copyright 2022 Linfeng Fan et al., published by Ivyspring International Publisher. d) Schematic illustration of cRGD/TPP@Res micelles releasing a long PEG chain to expose TPP at pH 5.0. Reprinted with permission from ref. [96]. Copyright 2023 American Chemical Society. e) Schematic illustration showing the microenvironment-responsive injectable conductive GOMW hydrogels for the regeneration of spinal cord damage. Reprinted with permission from ref. [97]. 2024 Wiley-VCH GmbH.

cause of AD may be a chemical imbalance of acid-base (or pH) present in the intracellular body.[95] Resveratrol polarises M1 microglia to an anti-inflammatory M2 phenotype, thereby exerting neuroprotective effects for the treatment of ischaemic stroke. However, obstruction of the BBB severely affects the efficacy of resveratrol. To overcome the hindrance of resveratrol crossing BBB, Wang et al.[96] developed a stepwise-targeted nanoplatform for enhanced ischemic stroke therapy, which was made of pH-responsive poly (ethylene glycol)-acetaldehyde-polycaprolactone-poly (ethylene glycol) (PEG-Acetal-PCL-PEG) and modified with cRGD and triphenylphosphine (TPP) on the long PEG and short PEG chains, respectively (Figure 6d). The designed micellar system achieved effective BBB penetration through cRGD-mediated transcytosis. Once inside the ischemic brain tissue and endocytosed by microglia, the long PEG shells are separated from the micelles in acidic lysosomes, and TPP is subsequently exposed

to target mitochondria. Furthermore, inspired by the unique acidic microenvironment at the site of acute spinal cord injury (SCI), Liu et al. designed an injectable conductive hydrogel with pH-responsive immunomodulation for SCI repair. This composite hydrogel, consisting of gelatin methacryloyl, oxidized dextran, and MoS2, has tunable mechanical and conductive properties based on dynamic Schiff base chemistry and covalent photocrosslinking that match the properties of the natural spinal cord (Figure 6e).[97] When the pH in the intracellular body is low the intracellular environment becomes too acidic and transported substances become trapped in the intracellular body that resides deep within the cell, while when the contents of the intracellular body are more alkaline, transported substances remain on the cell surface for too long. Therefore, using a PH-responsive drug delivery system can regulate the acid-base imbalance in AD, improve its internal environment, and promote normal substance metabolism. Overall, the development of endogenous stimuli-responsive nanocarrier systems for the CNS holds great potential for improving the treatment of neurological diseases. By leveraging the unique physiological and pathological conditions of the CNS, these systems can enhance drug delivery, increase therapeutic efficacy, and reduce adverse effects, paving the way for more effective treatments for CNS disorders.

4.1.2. Active Delivery Strategies for Nanocarriers

In recent years, active delivery strategies based on nanocarriers have become a hot research topic in the biomedical field due to their precise and controllable drug delivery ability. Compared with the traditional passive delivery strategy, active delivery significantly improves delivery efficiency and reduces systemic toxicity by directing the nanocarriers to the focal area through exogenous physical stimuli (e.g., magnetic field, ultrasound, photothermal). In recent years, active delivery strategies based on external magnetic fields have received extensive attention from researchers.

Magnetic nanoparticles can be directed to specific sites within the CNS using external magnetic fields, allowing for targeted drug delivery. Among all the response types, magnetically responsive nanomaterials have high overall performance and biosafety and can be regulated by external magnetic fields, so they have a broad application prospect. In addition, the magnetic properties of magneto-responsive nanomaterials can be used as a perfect link in the drug delivery system to improve the therapeutic efficacy by controlling the concentration of drug/biofactor-loaded magneto-responsive nanomaterials in local tissues through the targeted control of an external magnetic field. For instance, Li et al. fabricated a biomimetic nanocarrier consisting of a natural platelet (PLT) membrane envelope loaded with l-arginine and γ-Fe_2O_3 magnetic nanoparticles (PAMNs) for thrombus-targeted delivery of l-arginine and in situ generation of nitric oxide (NO) (**Figure 7a–f**).[98] The results showed that the designed 200 nm PAMNs inherited the natural properties of PLT membranes and achieved rapid targeting of ischemic stroke lesions under the guidance of an applied magnetic field. After the release of l-arginine at the thrombus site, endothelial cells produced NO, which promoted vasodilation and disrupted local PLT aggregation. Using magnetically responsive materials, the nanocarriers can be guided to specific brain sites by applying an external magnetic field, thus releasing the drug at the focal site to exert therapeutic effects, which has a promising application in drug delivery for ND. Besides, another researchers designed a magnetically guided robotic system for intracranial cross-scale targeted drug delivery by integrating a chemical/magnetic hybrid nanorobot and a miniature magnetic continuum robot.[99] To achieve primary targeting at the macroscopic scale, the continuum robotic system enters the cranial cavity through a minimally invasive channel in the skull and delivers the nanorobot to the disease-causing region. After bypassing the BBB, the released magnetical robotic system perform secondary targeting at the micrometer scale, further improving the spatial resolution of drug delivery.

In addition, Hongyue Zhang and his group designed a neutrophil-based micro-robot that can actively deliver cargo to malignant gliomas in vivo (**Figure 8a**).[100] Similarly, Ye et al. developed a biomimetic self-propelled nanomotor with cascade targeting capabilities for the treatment of neurological inflammatory diseases (Figure 8b).[101] The nanomotor mimics the structure of natural cell membranes and achieves multistage targeting by surface modification with dual-targeting ligands. The nanomotor mimics the structure of natural cell membranes and is surface-modified with dual-targeting ligands for multistage targeting delivery. The nanomotor mimics the structure of natural cell membranes and achieves multistage targeting delivery by surface modification of dual-targeting ligands. The nanomotor mimics the structure of natural cell membranes and achieves multistage targeting delivery by surface modification of dual-targeting ligands. Self-propulsion is achieved with the support of external energy to enhance the penetration ability in the brain, which not only targets the BBB, but also accurately localizes neuroinflammatory lesions.

4.2. Self-Assembled Drug Monomer-Based Drug Delivery

Self-assembly is the formation of ordered structures mediated by biochemical interactions, resulting in the formation of monomeric complexes including amphiphilic molecules, aromatic group-containing molecules, proteins, polymers, and inorganic nanoparticles.[102] Self-assembly is mainly driven by non-covalently bonded molecular interactions including electrostatic attraction, hydrogen bonding, π-π stacking interactions, van der Waals forces, and hydrophobic interactions.[103] Compared to the limited drug loading form using nanomaterial carriers, the self-assembly of drugs has the advantage of achieving 100% high drug loading. In addition, the self-assembly of different drug molecules through non-covalent forces can optimize the efficacy of single molecules through synergistic effects, reduce toxicity, and enhance transmembrane capacity, which can be synergistic in the treatment of diseases.[104]

In the treatment of brain injury, in order to break through the limitation of the therapeutic effect of a single drug on TBI, Wang Yang's team prepared a multicomponent self-assembled hydrogel system consisting of rhubarbic acid – canthaxanthin – glycyrrhizic acid traditional Chinese medicine small molecules (**Figure 9a**). The multi-component hydrogel was completely self-assembled from a variety of natural small molecules of traditional Chinese medicines without the involvement of exogenous inactive components or metal ions and had injectability

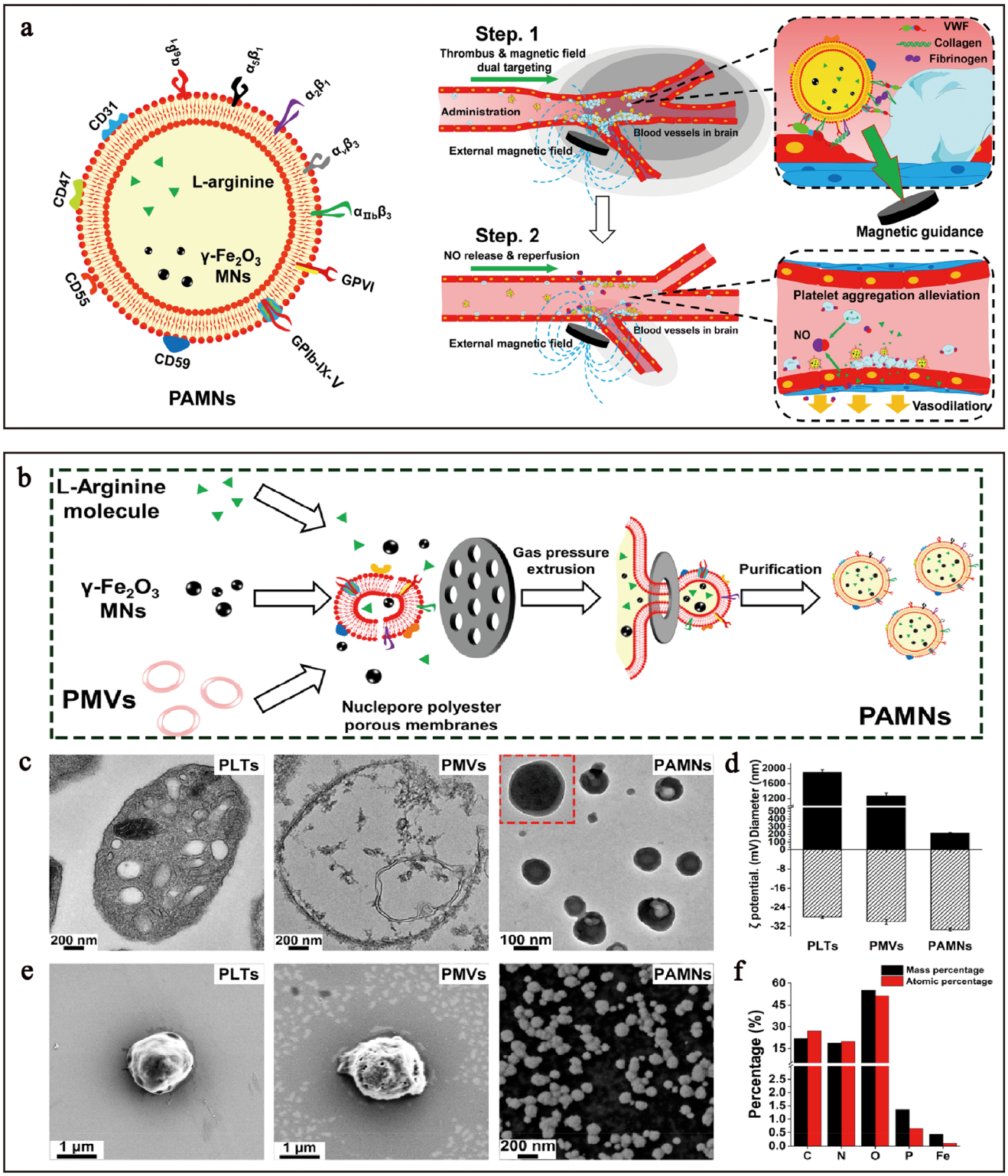

Figure 7. Representative magnetic response drug delivery. a) Schematic diagram of platelet membrane envelope loaded with l-arginine and γ-Fe2O3 magnetic nanoparticles (PAMNs) structure and in vivo targeting modalities. b) Schematic diagram of the preparation of PAMNs by the extrusion method. c) Transmission electronic microscopy characterization showing the internal structure of natural platelets (PLTs), platelet membrane vesicles (PMVs), and PAMNs. d) Hydrodynamic diameter and surface ζ potential of PLTs, PMVs, and PAMNs ($n = 3$). e) Scanning electron microscopy characterization showing the surface structure of PLTs, PMVs, and PAMNs. f) Quantitative elemental analysis results of PAMNs by energy dispersive spectroscopy (EDS). Reprinted with permission from ref. [98]. Copyright 2020 American Chemical Society.

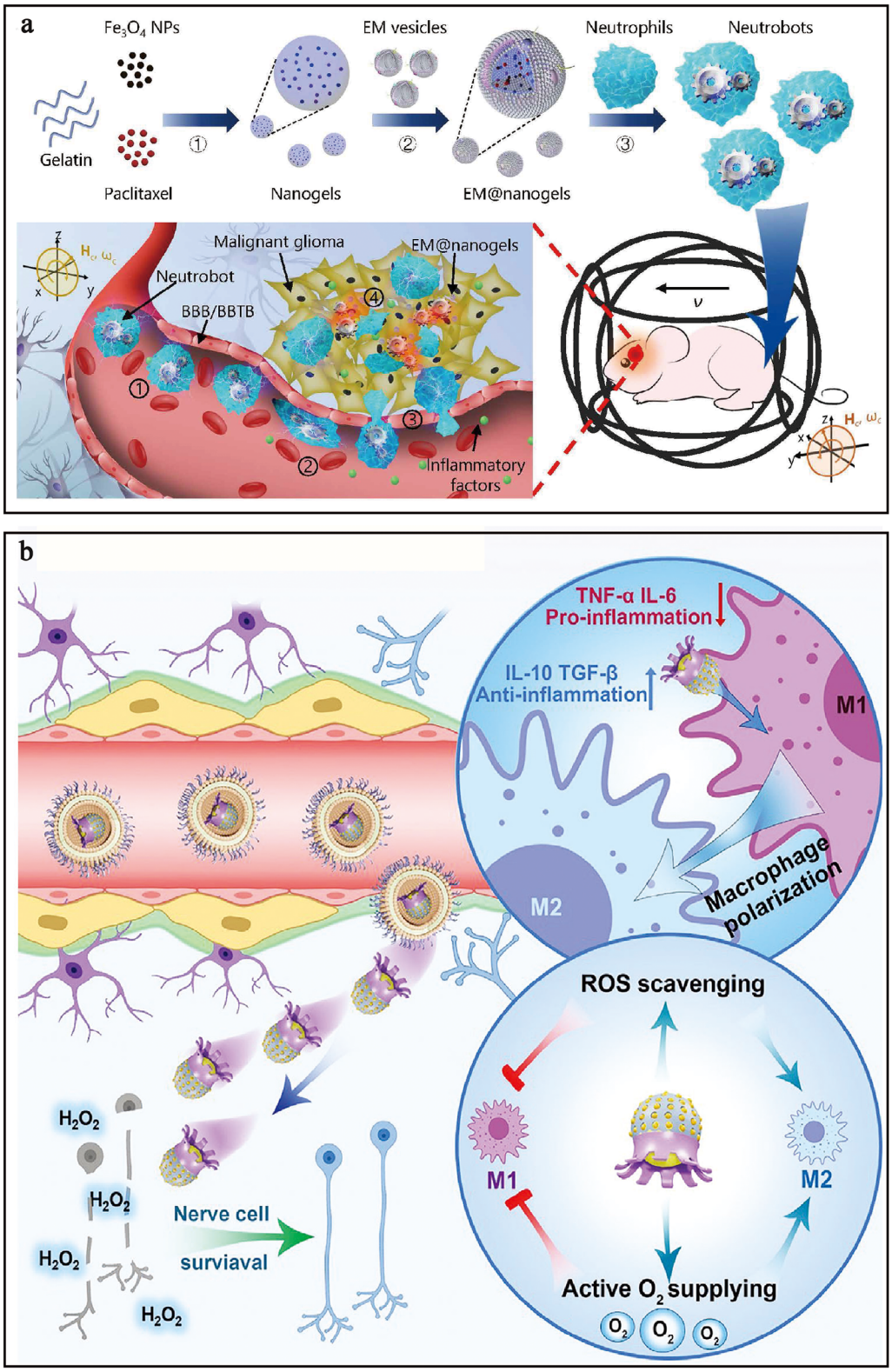

Figure 8. Representative drug-delivery strategies of Micro/Nano Robotics. a) Schematic of the active therapeutic approach of dual-responsive neutrobots in vivo. Reprinted with permission from ref. [100]. Copyright 2021 American Association for the Advancement of Science. b) Schematic illustration of the process of nanomotor cascade-targeting anti-inflammatory therapy. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [101]. Copyright 2024 Jiamin Ye et al., published by Wiley-VCH GmbH.

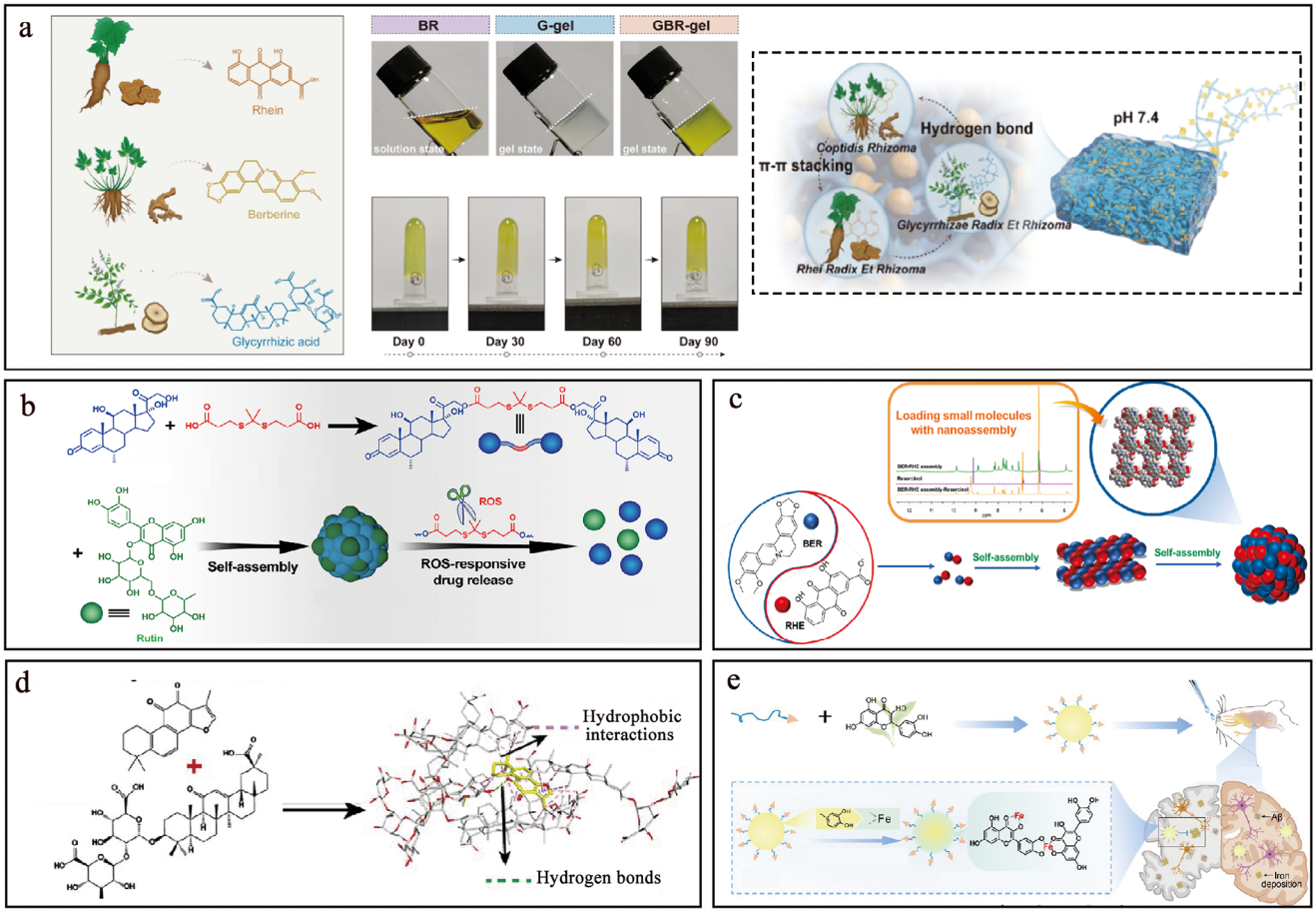

Figure 9. Representative drug-delivery strategies of Self-assembly. a) Characterizations of GBR-gel. Chinese medicine images of Rhei Radix Et Rhizoma, Coptidis rhizoma, and Glycyrrhizae Radix Et Rhizoma and chemical structures of rhein, berberine, and glycyrrhizic acid. Representative images of the BR particle solution, G-gel, and GBR-gel. Images of the same GBR-gel at room temperature for different times. Reprinted with permission from ref. [105]. Copyright 2024 The Authors and American Chemical Society. b) Schematic Illustration of the Synthesis and Preparation of the Carrier-Free Nanodrug MP2-TK@RU NPs. Reprinted with permission from ref. [106]. Copyright 2023 American Chemical Society. c) Self-assembly process and mechanism of BER-RHE assembly. Reprinted with permission from ref. [107]. Copyright 2022 Elsevier B.V. d) The self-assembly process for TanIIA and GL molecules. Reprinted with permission from ref. [108]. Copyright 2023 American Chemical Society. e) Schematic of mitochondria-targeted QC-derived intelligent nanochelator (TQCN) capable of self-assembling into metal–phenolic nanocomplexes in situ. Reprinted with permission from ref. [109]. Copyright 2023 American Chemical Society.

and optimal meningeal volume suitability. The results showed that the GBR gel exhibited excellent anti-inflammatory activity and effectively alleviated secondary brain edema after TBI.[105] In addition, to reduce the serious side effects associated with high-dose methylprednisolone administration, Mei-Wan Chen's team developed a nanoparticle-based on a co-assembly method of methylprednisolone bi-drugs and rutin. Two methylprednisolone molecules were connected by a thioredoxin bond to prepare a methylprednisolone double drug with reactive oxygen species (ROS)-responsive release (Figure 9b). The nanomedicine was ROS-responsive, which improved the targeting of the drug to the spinal cord injury site, and showed good anti-inflammatory and antioxidant activities in in vivo and in vitro experiments, which attenuated the damage of the neural tissues in SCI rats.[106] Aiming to overcome the limitations associated with single-target therapies, Kim and his group took a significant step forward in this direction by developing nano-delivery systems for two drugs. They utilized berberine (BER) and rhein (RHE) (Figure 9c), which are primary bioactive compounds derived from Coptis chinensis and rhubarb, respectively. These compounds were synthesized into carrier-free nanoassemblies with intricate 3D porous framework crystal structures.[107] In order to simultaneously deliver pure drug nanomicelles and immune adjuvants for safe and efficient GBM chemotherapy and immunotherapy, Cui et al. self-assembled tanshinone IIA (TanIIA) and glycyrrhetinic acid (GL) into tanshinone IIA-GL nanoparticles (TGM) (Figure 9d). Then, endogenous serum exosomes were selected to encapsulate pure drug nanoparticles, and CpG oligonucleotides, agonists of Toll-like receptor 9, were anchored onto the exosome membrane to obtain immune exosomes loaded with self-assembling nanoparticles of traditional Chinese medicine (CpG EXO/TGM). The research results indicate that CpG EXO/TGM can bind to free transferrin in the blood, prolong blood circulation, and maintain its intact structure when crossing the BBB and targeting GBM cells.[108] Furthermore, Liu et al.[109] developed a self-assembled phytopolyphenol-coordinated intelligent nanotherapeutics called

TQCN for the multipronged treatment of AD (Figure 9e). TQCN exploits its good brain-targeting and mitochondrial-localization properties to efficiently chelate iron through spontaneous ligand mediated by plant polyphenols and self-assembles in situ into metallic phenolic nanocomplexes to exert escalating exogenous attacking effects to alleviate iron overload and its induced free radical burst. In conclusion, self-assembled carrier-free nanomedicines can improve drug delivery efficiency and reduce adverse reactions due to their high drug loading capacity, low toxicity, easy synthesis method, and nanopreparations based on the self-assembly strategy of drug molecules can be constructed as a delivery system through self-assembly properties. In addition, the self-assembly strategy of multiple active ingredients enables multilevel targeting of neurological diseases and microenvironmental modulation of lesions.

5. Route of Administration

The CNS is highly protected by physiologic barriers, particularly the BBB which limits access to most drugs. Common routes of administration in the CNS include systemic administration, invasive localized administration such as intrathecal and parenchymal administration, and alternative routes of administration such as intranasal administration. Each route of administration has a different rate of absorption. Different routes of administration affect the absorption and bioavailability of the drug. Systemic administration such as oral and intravenous is less bioavailable and is suitable for drugs with good BBB permeability. Oral administration remains the primary clinical route for CNS drug delivery due to its non-invasiveness and patient compliance, exemplified by levodopa for PD, aspirin for stroke prevention, and carbamazepine for epilepsy.[110–112] However, gastrointestinal degradation and hepatic first-pass metabolism limit bioavailability, restricting its use to small, stable molecules with adequate BBB permeability. Intravenous (IV) injection enables rapid systemic drug distribution, critical for acute neurological conditions. However, this route of administration also presents the challenge of an elevated risk of adverse drug reactions, which may be further increased by the higher concentration of the intravenously administered drug upon entering the bloodstream directly. Most CNS drugs require formulation optimization for IV use. However, clinical translation remains challenged by biocompatibility and scalability. IV routes dominate acute care but necessitate rigorous safety monitoring, emphasizing the need for targeted delivery systems to balance efficacy and toxicity.

Invasive localized administration, such as intrathecal and intraparenchymal administration, allows the drug to enter directly into the subarachnoid space or intracerebral compartment of the brain and spinal cord compared to the conventional routes of administration (oral and intravenous). The blood-brain spinal cord barrier can be effectively circumvented, and the therapeutic effect of the drug can be realized directly. intrathecal administration delivers drugs directly into (CSF to bypass the BBB, primarily for leptomeningeal metastases. Intrathecal chemotherapy achieves high CSF concentrations with minimal systemic toxicity, historically vital pre-targeted therapies. While effective for CSF-localized tumors, its clinical utility is limited by invasiveness (lumbar puncture risks) and narrow applicability to neuro-oncology. Current use focuses on refractory cases or adjunct therapy, with ongoing optimization of drug stability and catheter systems to reduce complications. Intraparenchymal injection delivers drugs directly into brain tissue, enabling localized therapy for well-defined CNS lesions. While effective in preclinical models, its clinical use remains limited to rare cases due to procedural risks (surgery, infection) and poor scalability. Intraparenchymal injection exemplifies precision but prioritizes non-invasive routes unless lesion localization demands direct intervention. In addition, alternative routes of administration, such as intranasal administration, are important for the intervention and treatment of ND and can bypass the BBB and directly enter the CNS. Intranasal administration bypasses the BBB via olfactory pathways has some unique advantages, such as rapid onset of action, low side effects, and the ability of the patient to self-administer the drug. The nasal cavity is rich in vascular plexus, and the surface area of nasal mucosa is large, containing many microvilli, which increases the effective area for drug absorption. Drugs delivered by intranasal drug delivery can enter the bloodstream directly and avoid digestive damage and first-pass effect, improving the bioavailability and kinetics of drugs. Second, the nasal cavity is in close proximity to the brain and has the capacity to traverse the BBB, thereby facilitating direct access to the brain. Various routes of administration in CNS are shown in **Figure 10**. The administration of drugs to the CNS needs to be based on the characteristics of various CNS diseases, taking into account the drug's own metabolic characteristics and BBB permeability, and appropriately selecting the route of administration in order to achieve the best therapeutic effect.

The efficacy of diverse drug delivery strategies and administrations depends on its ability to synergize with the pathological features of specific diseases. The following sections will explore how these strategies are tailored to address the unique challenges of major ND, emphasizing the interplay between delivery mechanisms and disease pathophysiology. This transition underscores the importance of precision in matching delivery methods to clinical needs.

6. The Application of Drug-Delivery Strategies for Drug Therapy of Major Neurological Disorders

6.1. The Application of Drug-Delivery Strategies for Drug Therapy of Ischemic Stroke

Ischemic stroke results in significant neurological impairment, particularly in the context of acute ischemic stroke, where rapid vascular obstruction leads to extensive neuronal death. The primary objective in the treatment of an ischemic stroke is to safeguard and salvage neurons within the ischemic semi-domain. Prompt recanalization therapies, such as intravenous thrombolysis and endovascular thrombolysis, have demonstrated efficacy. However, their application is constrained by the therapeutic window and the risk of bleeding. Neuroprotectants have demonstrated the potential to extend the therapeutic window in animal models; however, their clinical efficacy is constrained by several factors, including their short half-life, low bioavailability, inability to cross the BBB, and potential toxicity to the liver and kidneys. The limited efficacy of most anti-stroke drugs is largely due to

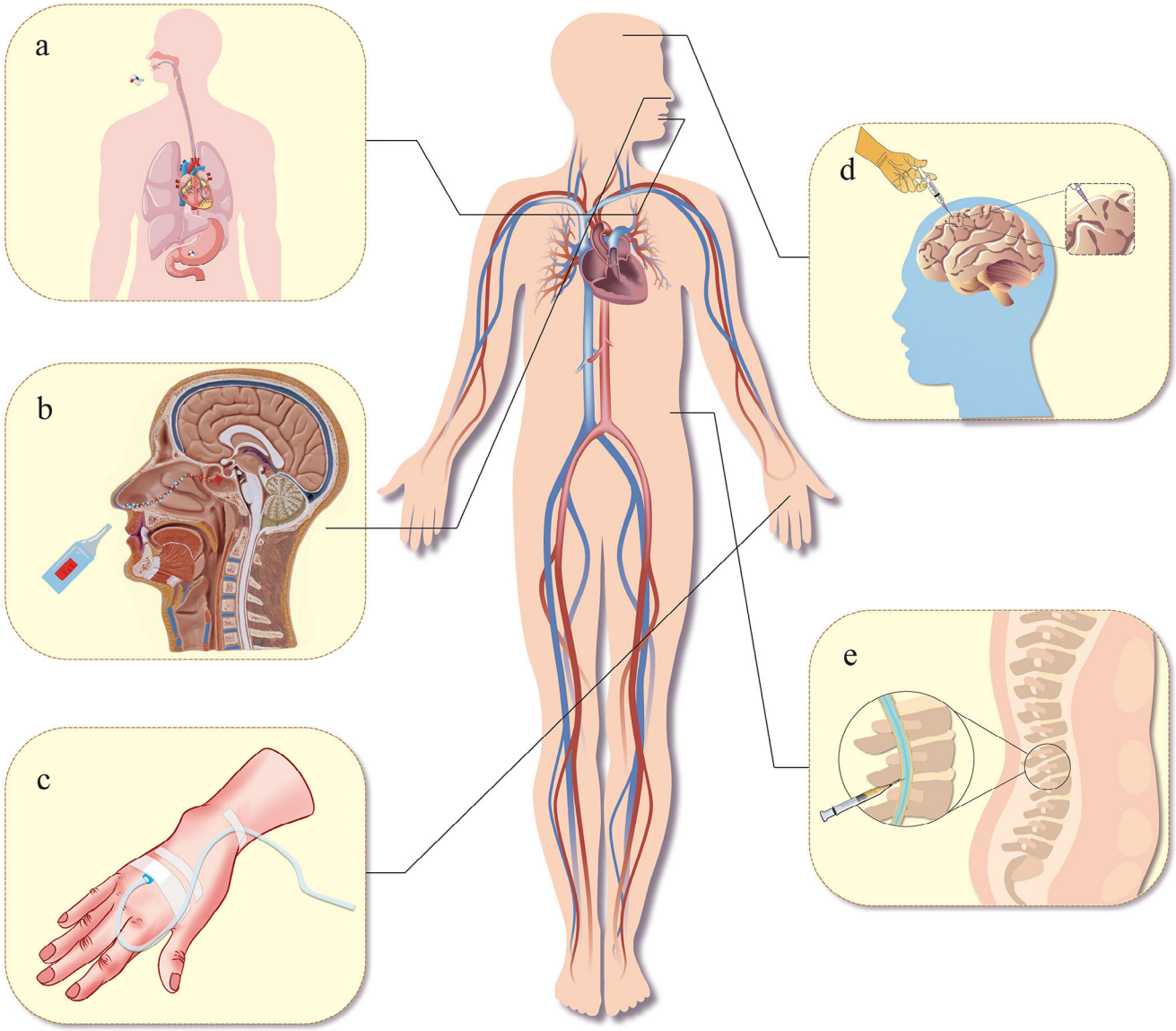

Figure 10. Various routes of administration in central nervous system. a) Gastrointestinal administration. b) Intranasal delivery. c) Intravenous injection. d) Intraparenchymal injection. e) Intraparenchymal injection.

inadequate drug delivery to ischemic lesions, which is impeded by the BBB.

The exploration of innovative drug delivery strategies represents a crucial avenue for enhancing drug stability, facilitating modification, controlling the release rate of drugs, improving biofilm permeability, prolonging the duration of action, and reducing the number of administrations. This approach holds immense promise for advancing the efficacy of drug therapy, particularly in the context of neuroprotective drugs for ischemic stroke. The drug-delivery strategies used in the drugs for the treatment of ischemic stroke are systematically summarized (**Table 1**). Fingolimod hydrochloride (FTY720) is an anti-inflammatory agent approved by the Food and Drug Administration (FDA) that has shown potential neuroprotective effects in ischemic brain parenchyma. However, it remains challenging to deliver sufficient amounts of FTY720 across the BBB into brain lesions without causing severe cardiovascular side effects. To address this issue, Zhao et al.[113] designed a neutrophil membrane-camouflaged multi-pre-drug nanomedicine that could migrate into ischemic brain tissues and release FTY720 in situ in response to elevated levels of ROS in the lesion (**Figure 11a**). This nanomedicine delivered more than 15.2-fold more FTY720 to the ischemic brain and significantly reduced the risk of cardiotoxicity and infection compared to intravenously injected free drug. Inadequate drug delivery to ischemic lesions impeded by the BBB largely limits the therapeutic efficacy of most anti-stroke drugs. Inspired by the rapid BBB penetrability of 4T1 tumor cells during brain metastasis and the natural role of platelets in targeting damage to the chorioallantoic system, Tang et al.[114] developed a biologically derived nano-jacket, which was further encapsulated on the surface of liposomes loaded with paeonol and polymetformin to obtain a biomimetic nanoplatform (PP@PCL) for

Table 1. Drug-delivery strategies used in solving these challenges of drugs for the treatment of ischemic stroke (IS).

ND	Drugs	Challenges	Drug-delivery strategies	Administration	Refs.
IS	Fingolimod hydrochloride	BBB	Neutrophil membrane-camouflaged multi-pre-drug nanomedicine and ROS response	Intravenous injection	[113]
IS	Paeonol and polymetformin	BBB and poor targeting	Biomimetic nanoplatforms by fusing 4T1 tumor cell membrane with platelet membrane	Intravenous injection	[114]
IS	Curcumin (Cur) and edaravone (EDV)	Short half-life	Supramolecular peptide hydrogel by co-assembling Cur and EDV	Intraparenchymal injection	[115]
IS	Curcumin	BBB	Nanoparticles loaded with curcumin and functionalized with rabies virus glycoprotein (RVG29)	Intravenous injection	[116]
IS	Apelin-13	BBB	Nanoparticle delivery system (MM/ANPs) using macrophage membranes encapsulated with DSPE-PEG-RVG29 peptide, which effectively delivered Apelin-13	Intravenous injection	[117]
IS	Atorvastatin	Poor targeting	Atorvastatin-loaded ROS-responsive chitosan-bilirubin (ChiBil) nanoparticles	Intravenous injection	[118]
IS	Hirudin	Brief half-life and potential adverse effects	PH-sensitive hirudin-loaded antioxidant nanoparticle formulation	Intravenous injection	[119]

ischemic stroke therapy. This PP@PCL significantly alleviated ischemia-reperfusion injury by effectively targeting ischemic lesions, preventing neuroinflammation, scavenging excess ROS, reprogramming microglia phenotype, and promoting angiogenesis (Figure 11b). Nanocarriers based on biomimetic modifications of leukocyte or platelet membranes enable passive BBB traversal by mimicking natural cell migration behavior, and their ROS-responsive properties allow precise drug release into the ischemic semidarked zone. Such strategies show significant brain drug accumulation enhancement in animal models, but the key challenge is the stability of the modified membrane proteins. Notably, over-infiltration of neutrophils in the acute phase may exacerbate the inflammatory response, leading to "hijacking" of the nanocarriers to non-targeted areas such as the heart. In addition, the dual-targeting design of platelet membrane targeting to the site of injury and RVG29 peptide-enhanced BBB penetration significantly increased the focal drug concentration up to several-fold, but cautioned against the risk of long-term immunogenicity.

Curcumin (Cur) and edaravone (EDV) have shown significant therapeutic effects in ischemic stroke. However, their short half-life and poor water solubility limit their use for effective long-term neuroprotection. In order to maximize the synergistic therapeutic effect of the two drugs, Jia et al.[115] prepared a novel supramolecular peptide hydrogel (EDV/Cur/NapFFY) by co-assembling Cur and EDV with a well-studied hydrogel agent, Nap-Phe-Phe-Tyr-OH (NapFFY), which can improve their bioavailability and precisely deliver hydrophobic drugs to the ischemic site through local administration (Figure 11c). In vitro release tests showed that co-assembly with NapFFY resulted in sustained release of Cur and EDV for approximately two weeks. In animal studies, EDV/Cur/NapFFY hydrogels were found to be effective in promoting brain plasticity and enhancing functional recovery in a mouse model of photothrombosis. This strategy is particularly suitable for patients undergoing craniotomy, but the matching of hydrogel degradation kinetics to the brain tissue repair cycle still needs to be validated. Yang et al.[116] employed gelatin nanoparticles loaded with curcumin and functionalized with rabies virus glycoprotein (RVG29) to target brain tissue, thereby addressing the limitations of curcumin, including poor water solubility and BBB transmembrane permeability. The results demonstrated that the prepared nanoparticles enhanced the solubility and BBB permeability of Cur, markedly reduced neuroinflammation, diminished neuronal apoptosis, and largely restored behavioral functions. Similarly, in order to deliver apelin-13 (APN) with potent antioxidant, anti-apoptotic, and anti-inflammatory properties through the BBB into the inflammatory site of cerebral ischemic injury, Ma et al.[117] developed a functional nanoparticle delivery system using macrophage membranes encapsulated with DSPE-PEG-RVG29 peptide, which effectively delivered Apelin-13 to the inflammatory region for the treatment of ischemic stroke. The experimental results demonstrated that MM/ANPs were capable of effectively traversing the BBB and accumulating in ischemic and inflammatory regions in a selective manner. In a mouse model of ischemic reperfusion injury, these nanoparticles were observed to significantly enhance neurological scores and reduce infarct size.

Oxidative stress is a key mechanism leading to brain damage from cerebral ischemia/reperfusion. The brain is highly susceptible to ROS, and ROS generated by ischemia/reperfusion aggravate neuronal and BBB damage, leading to inadequate nutrient supply and a cascade of reactions such as increased lipid peroxidation and neuronal cell death. Therefore, targeted intervention in the ROS-induced cerebral ischemia/reperfusion process can improve efficacy in the target brain region while minimizing systemic side effects. Nagareddy et al.[118] developed ROS-responsive ChiBil nanoparticles loaded with atorvastatin (ChiBil-Statin) for targeted delivery to the ischemic brain and synergistic effects by combining neuroprotective agents. The results showed that intravenous injection of ROS-responsive multifunctional ChiBil-Statin could effectively deliver the drug to the ischemic brain, exerting a significant synergistic multi-biological neuroprotective effect. In a separate study, the issues associated with hirudin, including its brief half-life and potential adverse effects such as excessive ROS-induced ICH, were examined with the aim of enhancing the limitations of hirudin's short half-life in vivo and

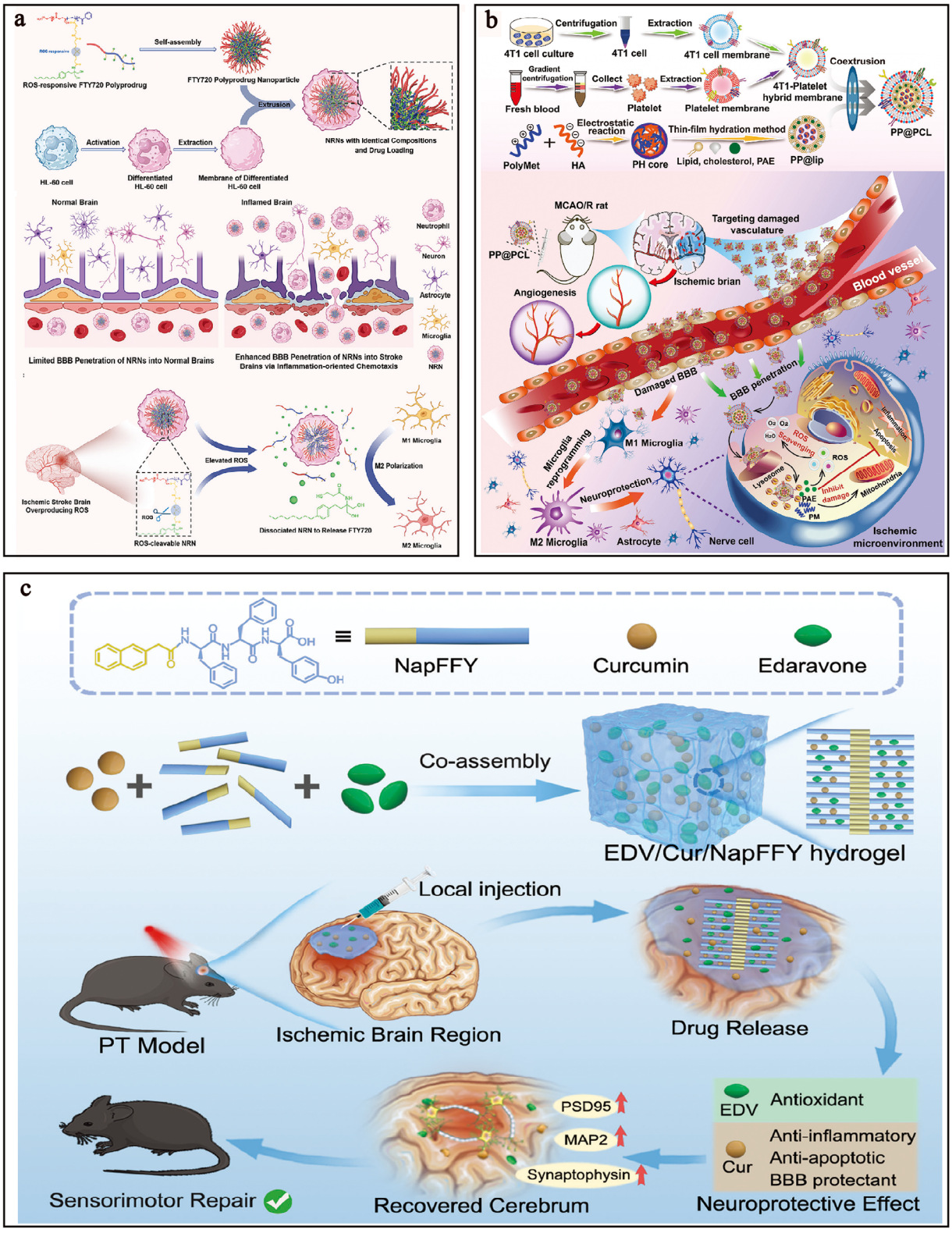

Figure 11. The application of drug-delivery strategies for the treatment of ischemic stroke. a) Schematic illustration of the formation and anti-inflammation effects of NRNs. Reprinted with permission from ref. [113]. Copyright 2024 Wiley-VCH GmbH. b) Schematic illustration of the preparation of PP@PCL NPs and therapeutic mechanisms of PP@PCL NPs for precise ischemic stroke management. Reprinted with permission from ref. [114]. Copyright 2024 Wiley-VCH GmbH. c) Schematic illustration of the preparation process of EDV/Cur/NapFFY hydrogel and the EDV/Cur/NapFFY hydrogel promoting nerve recovery in stroke mice model. Reprinted with permission from ref. [115]. Copyright 2023 Wiley-VCH GmbH.

reducing the risk of hirudin-induced hemorrhagic complications. To address these challenges, Ting Mei's team devised a novel pH-sensitive hirudin-loaded antioxidant nanoparticle formulation (HD@iNano^{AOX}). The HD@iNano^{AOX} encapsulated hirudin within the hydrophobic PIC cores of the antioxidant nanoparticles, thereby preserving and prolonging the biological activity of hirudin. The nanoscale particle structure of this compound prevented stochastic internalization and damaged to normal tissues while facilitating penetration of the damaged BBB at the lesion site. It accumulated in the target area of cerebral infarction and the surrounding ischemic penumbra. The acidic microenvironment at the lesion site initiated the breakdown of the core of polyion complex, resulting in the gradual release of the encapsulated hirudin. This prolonged the half-life of hirudin within the body and enhanced the thrombolytic effect at the inflamed infarct site.[119] Utilizing ROS/pH abnormalities in the ischemic region to achieve intelligent drug release can increase the exposure of the lesion several times while reducing systemic toxicity. However, it should be noted that over-reliance on the pathologic microenvironment may lead to leakage of subthreshold injury regions. In addition, the temporal sequential relationship between ROS clearance and neuroprotection needs to be further clarified.

For ischemic stroke, drug-delivery strategies aim to overcome BBB limitations and enhance targeted efficacy. Bionic nanocarriers such as neutrophil/platelet membrane-modified systems achieve passive BBB penetration by mimicking cell migration and precisely release drugs by utilizing the ROS/PH response properties of the ischemic semi-dark band region, which can enhance drug accumulation in the brain. Hydrogel platforms extend drug action up to two weeks through localized slow release for craniotomy patients, but the synchronization of degradation and repair needs to be further investigated. ROS/pH-responsive nanoparticles leverage the pathologic microenvironment to achieve intelligent drug release, significantly enhancing lesion exposure and reducing systemic toxicity. Most of the current strategies are in the preclinical stage, and their translation needs to address the risk of immunogenicity, uncertainty in the targeting of subthreshold injury zones, and uncertainty in the mechanisms of ROS regulation related to the timing of neuroprotection.

6.2. The Application of Drug-Delivery Strategies for Drug Therapy of Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is a neurological disorder caused by non-traumatic intracerebral blood vessel rupture. Occupancy effects, brain tissue destruction, and increased intracranial pressure caused by hematomas following ICH leads to primary brain damage following ICH.[120,121] Subsequently, excitotoxicity, perihematomal edema, and iron release from erythrocyte lysis cause secondary brain damage.[122] Despite the existence of a number of drugs that demonstrate therapeutic effects in the context of ICH, the majority of these drugs exhibit poor bioavailability, a consequence of their low solubility and the occurrence of off-target effects. The presence of the BBB also limits the entry of therapeutic agents into the brain and affects the efficacy of these drugs. In addition, the effective delivery of drugs to the site of injury following ICH has thus become a challenge that needs to be addressed. For instance, trans-resveratrol has been shown to possess a variety of biological activities, including anti-inflammatory and antioxidant effects. Nevertheless, the low water solubility of trans-resveratrol curtails its therapeutic application in ICH. In order to address these limitations, Banshoya et al.[123] developed a water-soluble micellar formulation containing resveratrol using polyethylene glycol monostearate (stPEG), which encapsulates resveratrol within the internal hydrophobic portion of the micelle. Experimental findings demonstrated that intravenous injection of stPEG/Res enhanced neurological and motor function recovery in a collagenase-induced ICH mouse model.

Curcumin has been identified as a promising agent for the treatment of ICH due to its multiple biological activities. However, its application is limited by its poor aqueous solubility and instability. Consequently, a team of researchers prepared platelet membrane-encapsulated curcumin polylactic acid-glycolic acid (PLGA) nanoparticles (PCNPs) to significantly improve the solubility, stability, and sustained release of curcumin. PCNPs were used to treat ICH in rats by tail vein injection. The experimental results demonstrated that the PCNPs had a good targeting effect on the site of the hemorrhage.[124] In a separate study, researchers sought to enhance the brain-penetrating capacity of curcumin by employing a mPEG-PCL encapsulation technique to formulate curcumin nanoparticles. These nanoparticles were then delivered directly from the nasal cavity to the brain via an intranasal route of administration (**Figure 12a**). This approach led to the amelioration of BBB damage in ICH mice and the promotion of recovery of neurological function after stroke.[125] In addition, Duan et al. constructed minocycline (MC)-loaded cerium oxide nanoparticles (CeO2-MC) for the combined treatment of ICH. Ultrasmall CeO2 synthesized by a high-temperature method possessed strong free radical scavenging and iron chelating abilities. In vitro experiments showed that CeO2-MC was effective in reducing ROS levels in mouse microglial cells and neurons when stimulated by oxyhaemoglobin. In addition, CeO2-MC possesses iron chelating properties and can stabilize the mitochondrial membrane potential, thus promoting anti-inflammatory responses and preventing neuronal iron sudden death (Figure 12b). In a mouse model of ICH, CeO2-MC exhibited potent free radical scavenging ability and demonstrated the ability to protect mitochondrial morphology and function, attenuate cerebral edema, and maintain the integrity of the BBB by inhibiting neuroinflammation and iron metabolism.[126] Activation of peroxisome proliferator-activated receptor γ (PPARγ) has a good therapeutic effect on haematoma clearance in ICH. In order to utilize this mechanism to improve the therapeutic effect, Wang et al.[127] synthesized a magnetic-targeted nanocarriers (15d-PGJ2-MNPs) loaded with PPARγ agonist, which could be magnetically targeted and enriched in the haematoma region after intravenous injection (Figure 12c). Subsequent application of FUS enhanced drug diffusion, which activated PPARγ receptors on macrophages around the haematoma for better clearance of the haematoma.15d-PGJ2-MNP treatment reduced brain injury, accelerated haematoma clearance, reduced neuroinflammation, and alleviated cerebral oedema in an ICH mouse model. This strategy utilizes magnetic targeting carriers to specifically target hematoma regions and significantly reduces hematoma volume in animal models, but the depth limitations

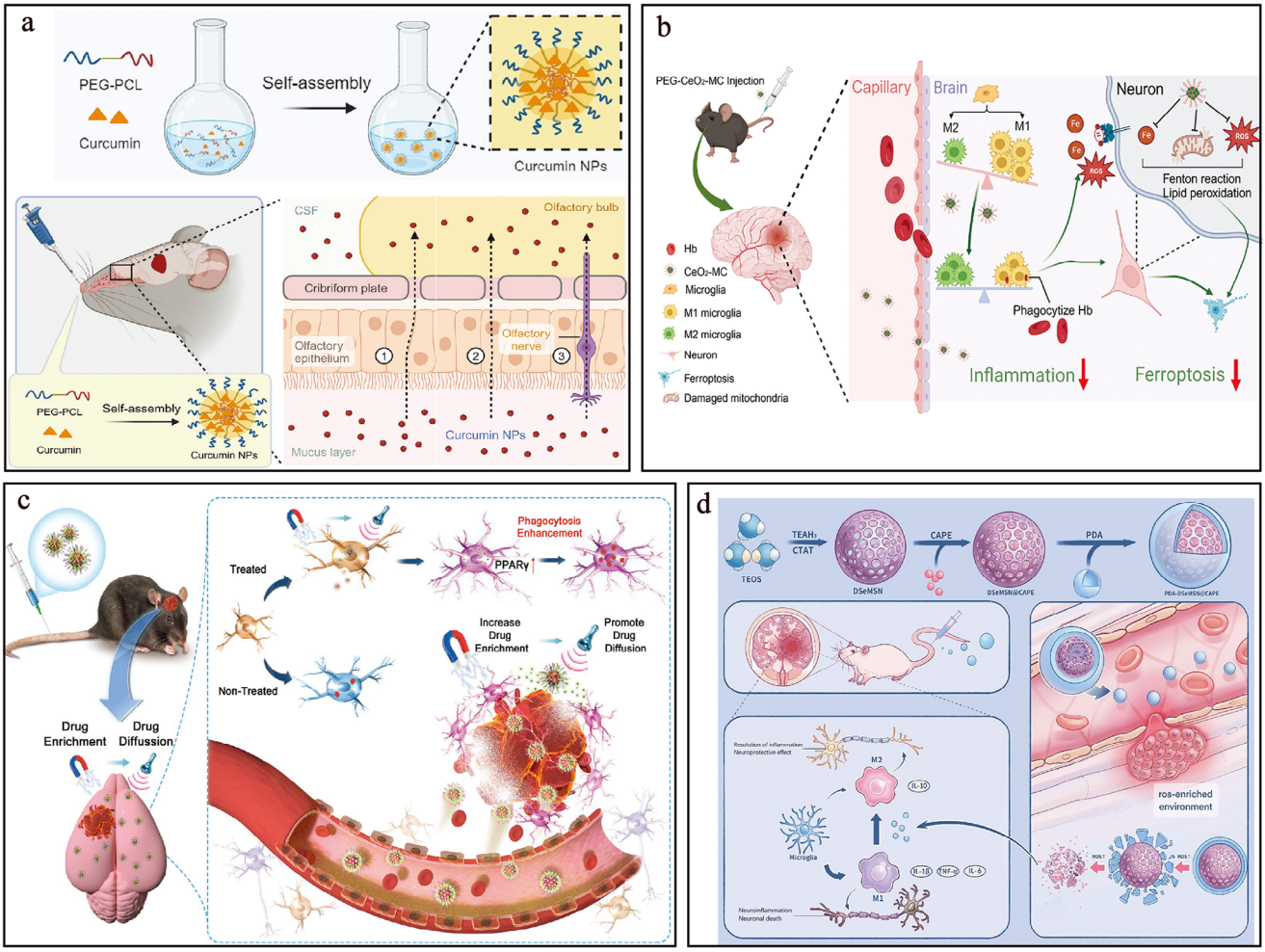

Figure 12. The mechanism of drug-delivery strategies for the treatment of intracerebral hemorrhage. a) Illustration diagrams of Curcumin nanoparticles intranasal administration in treating intracerebral hemorrhage mice by mitigating neuroinflammation and reducing neuron death. Reprinted with permission from ref. [125]. Copyright 2024 Wiley-VCH GmbH. b) Ultrasmall cerium oxide nanoparticles loaded with minocycline (CeO2-MC) synergistically exhibit anti-inflammatory properties and inhibit neuronal ferroptosis, thereby mitigating brain injury following intracerebral hemorrhage. Reprinted with permission from ref. [126]. Copyright 2023 Wiley-VCH GmbH. c) Schematic illustration of the hypothetical mechanism of 15d-PGJ2-MNP administration with the application of the magnet and focused ultrasound. Reprinted with permission from ref. [127]. Copyright 2023 Wiley-VCH GmbH. d) Schematic illustration of the fabrication process and the mechanism of PDA-DSeMSN@CAPE. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [128]. Copyright 2024 Fangfang Zhou et al., published by Springer Nature.

of magnetic targeting and the clinical suitability of FUS still need to be validated.

Oxidative stress and neuroinflammation represent pivotal pathological processes in secondary brain injury (SBI) subsequent to ICH. Their close interaction serves to trigger and exacerbate brain injury. In order to target these two pathological processes, Zhou et al.[128] developed a high-performance platform using polydopamine (PDA)-coated diselenide-bridged mesoporous silica nanoparticles (PDA-DSeMSN) as a smart ROS scavenger and a ROS-responsive drug delivery system. The PDA-DSeMSN @CAPE exhibited high stability and was found to be highly stable in hematoma. The PDA-DSeMSN @CAPE demonstrated high stability and underwent ROS-responsive degradation and drug release around the hematoma (Figure 12d), effectively eliminating ROS and suppressing neuroinflammation in vitro and in vivo. Such strategies synergistically intervene to scavenge free radicals and ROS levels in cerebral hemorrhage and attenuate neuroinflammatory multipathological aspects. In another study, He et al.[129] constructed a novel polydopamine (PDA)-coated diselenide-bridged mesoporous silica nanoparticle (DSeMSN) drug delivery system (PDA-DSeMSN) to achieve both ROS scavenging ability and on-demand drug release ability. By covering the pores with PDA as a gatekeeper, edaravone (Eda) was blocked in the pores of DSeMSN. The drug maintains almost "zero release" until it reaches the site of the lesion. However, in the presence of ROS-enriched conditions, degradation of the PDA shell occurs and the doped diselenide bond is broken, triggering disintegration of the nanoparticles and resulting in the release of Eda. The accumulation of PDA-DSeMSN@Eda at the perihematoma site was observed after intravenous injection, and the drug exhibited potent neuroprotective effects in the ICH mouse model through antioxidant and anti-apoptotic effects.

Table 2. Drug-delivery strategies used in solving these challenges of drugs for the treatment of intracerebral hemorrhage (ICH).

ND	Drugs	Challenges	Drug-delivery strategies	Administration	Refs.
ICH	Resveratrol	BBB	Water-soluble micellar formulation containing resveratrol using polyethylene glycol monostearate	Intravenous injection	[123]
ICH	Curcumin	Low stability and BBB	Platelet membrane-encapsulated curcumin polylactic acid-glycolic acid (PLGA) nanoparticles	Intravenous injection	[124]
ICH	Curcumin	Low stability and BBB	A mPEG-PCL encapsulation technique to formulate curcumin nanoparticles	Intranasal delivery	[125]
ICH	Minocycline and cerium oxide	Requirement for high doses and combination therapy	Minocycline-loaded cerium oxide nanoparticles with surface modification with polyethylene glycol	Intravenous injection	[126]
ICH	PPARγ agonist	Poor targeting	Magnetic-targeted nanocarriers (15d-PGJ2-MNPs) loaded with PPARγ agonist	Intravenous injection	[127]
ICH	Polydopamine	Poor targeting	Platform using polydopamine (PDA)-coated diselenide-bridged mesoporous silica nanoparticles (PDA-DSeMSN) as a smart ROS scavenger and a ROS-responsive drug delivery system	Intravenous injection	[128]
ICH	Polydopamine and edaravone	BBB and poor targeting	Novel polydopamine (PDA)-coated diselenide-bridged mesoporous silica nanoparticle (DSeMSN) drug delivery system (PDA-DSeMSN) to achieve ROS scavenging ability and edaravone release	Intravenous injection	[129]

Drug delivery strategy provides a new approach for the treatment of ICH. The drug-delivery strategies used in the drugs for the treatment of ICH are systematically summarized (**Table 2**).

The therapeutic challenges of ICH arise from the BBB, hematoma occupancy, iron toxicity and oxidative stress-neuroinflammatory cascade. Nano-delivery systems break through conventional drug limitations by targeting the pathologic microenvironment. ICH drug-delivery studies are in the preclinical stage, and their translational potential is limited by the dynamic microenvironmental adaptability of the following factors: pH, ROS, and immune microenvironment of the post ICH hematoma region evolve over time, and the existing ROS/pH response systems are mostly designed for the acute phase and lack of temporal adaptability. In the future, it is necessary to develop "smart" delivery systems that can dynamically respond to pathological processes, and validate them with organoid and clinical samples to enhance translational feasibility.

6.3. The Application of Drug-Delivery Strategies for Drug Therapy of Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized by memory deficits and cognitive decline, which affects millions of people.[130] Only several drugs (i.e., rivastigmine, galantamine, and donepezil) have been approved by the FDA for the treatment of AD, and none of them can reverse or even slow the neuronal damage and destruction that leads to worsening AD symptoms.[131,132] Much of the reason for this is that these drugs have difficulty crossing the BBB to reach the lesion site. In addition, some drugs derived from plants and animals have been found to demonstrate therapeutic benefits in managing AD through various pathological mechanisms.[133] For instance, Resveratrol (Res), a highly active natural phytoalexin polyphenolic agent, has been shown to exhibit multiple biological effects, including antioxidant, anti-inflammatory, anti-apoptotic activities, and mitochondrial protection, which contribute to alleviating AD symptoms. In vitro studies have demonstrated Res's clear neuroprotective effects.[134] Nonetheless, its effectiveness in enhancing cognition in AD animal models is limited due to its low oral bioavailability (<1%), poor water solubility, limited chemical stability, and rapid metabolism. Additionally, vitamins C, E, and D have been shown to possess strong antioxidant properties relevant to AD, helping to reduce neuroinflammation and damage caused by oxidative stress to the brain.[135] Bryostatin enhances the activity of the α-Secretase enzyme, resulting in decreased Aβ production, lower mortality rates in AD mouse models, and improved learning and memory functions in mice.[136] Despite these advancements, challenges such as the BBB's restriction on drug transport, poor absorption in the digestive system and difficulties in reaching the brain, limit the therapeutic effectiveness of AD treatments.

Nano-delivery has become a promising tool for drug delivery in the CNS due to its capacity to regulate drug distribution to specific sites of action. Using nanoparticles, natural drugs have demonstrated an enhanced ability to cross the BBB and target the pathological mechanisms underlying disease conditions. Specifically, nanoparticle-mediated therapies utilizing drugs focus on addressing AD-related pathological processes, such as Aβ accumulation, tau pathology, cholinergic deficits, oxidative stress, inflammation, and mitochondrial dysfunction. Among these, targeting the production of Aβ stands out as a prevalent strategy in the development of nano-delivery systems for natural drugs. The drug-delivery strategies used in the drugs for the treatment of AD are systematically summarized (**Table 3**).

Recently, Andrade et al.[137] proposed using liposomes loaded with caffeic acid to overcome its chemical instability and limited bioavailability. By leveraging the overexpression of the transferrin (TF) receptor on brain endothelial cells, they attached TF to the surface of these liposomes to enhance the delivery of caffeic acid-loaded nanoparticles across the BBB. Their results revealed that TF-functionalized liposomes carrying caffeic acid were effective in inhibiting the aggregation and fibril formation of Aβ

Table 3. Drug-delivery strategies used in solving these challenges of drugs for the treatment of Alzheimer's disease (AD).

ND	Drugs	Challenges	Drug-delivery strategies	Administration	Refs.
AD	Caffeic acid (CA)/transferrin (Tf)	Low stability and BBB	CA-loaded Tf-functionalized liposomes	Intravenous injection	[137]
AD	Nicotinamide adenine dinucleotide (NAD+)	BBB and poor targeting	ROS-responsive nanoscavenger (P@NB) loaded with NAD+ and co-decorated with the Beclin1 and angiopoietin-2 (Ang2) peptides	Intravenous injection	[138]
AD	Astaxanthin (AST)	Low stability and BBB	AST-loaded stealth lipid nanoparticles	Intravenous injection	[139]
AD	Galantamine	BBB and potential adverse effects	Galantamine-loaded chitosan	Intranasal delivery	[140]
AD	6-amino-2-naphthalenesulfonic acid (ANA)	BBB and poor targeting	Porous silicon nanoparticles (pSiNPs) with biotin polyethylene glycol (PEG) surface modification	Intravenous injection	[141]
AD	Anthocyanin	BBB and poor targeting	Gold nanoparticles with polyethylene glycol (PEG) surface modification	Intravenous injection	[142]
AD	Resveratrol (Res)	Low stability and BBB	Res functional selenium	Intravenous injection	[144]
AD	Trehalose	BBB	Poly(trehalose) nanoparticle	Intravenous injection	[145]
AD	Berberine-Rhein (BER-RHE)	BBB	Self-assembly (BER-RHE)	Administration in vitro	[107]
AD	Salidroside (Sal) and icariin (Ica)	BBB and poor targeting	Liposomes with surface-modified with angiopep-2 (Ang-Sal/Ica-Lip)	Intravenous injection	[146]
AD	Icariin (ICA) and tanshinone IIA (TSIIA)	BBB and poor targeting	Long-circulating (Ang2-ICA/TSIIA) liposomes modified with animepep2	Intravenous injection	[147]

and could effectively promote the degradation of mature fibrils. In a separate study aimed at overcoming the challenges of low BBB permeability and non-selective induced autophagy by nicotinamide adenine dinucleotide (NAD+), a ROS-responsive nanoscavenger (P@NB) loaded with NAD+ and simultaneously decorated with Beclin1 and angiopoietin-2 (Ang2) peptides was constructed. This formulation allowed for the rapid release of NAD+ in areas with high ROS levels, enhancing mitochondrial autophagy flux, facilitating Aβ degradation, reducing inflammatory responses, and thus ameliorating cognitive deficits in AD mice (**Figure 13**a).[138] Furthermore, Shehata et al.[139] formulated nanostructured lipid carriers (AST-NLC) loaded with astaxanthin for AD rat treatment, which significantly reduced oxidative stress, amyloidogenic pathway activation, neuroinflammation and apoptosis, while enhancing cholinergic neurotransmission. In another study, the researchers explored the use of chitosan-based nanoparticles for the nasal delivery of galantamine hydrobromide (GH) to avoid the side effects of oral administration, such as gastrointestinal disturbances, nausea, and vomiting. The in vitro drug release experiments demonstrated that GH-loaded chitosan NPs achieved an extended-release of the drug over 8 h.[140]

To enhance the decomposition of Aβ plaques, a nano-platform incorporating 6-amino-2-naphthalenesulfonic acid (ANA), a compound noted for its superior efficacy in Aβ plaque decomposition, was developed. Utilizing porous silicon nanoparticles (pSiNPs) with biotin polyethylene glycol (PEG) surface modification, this platform was engineered to deliver a substantial quantity of ANA directly to the brain regions affected by AD and could significantly improve memory deficits in an AD mouse model by facilitating the breakdown of amyloid plaques (Figure 13b).[141] Additionally, Kim et al.[142] explored the neuroprotective effects of PEG gold nanoparticles (AuNPs) loaded with anthocyanins in AD models. The anthocyanin-conjugated PEG AuNPs demonstrated enhanced efficacy compared to anthocyanins alone, effectively inhibiting the p-JNK/NF-κB/p-GSK3β pathway and reducing Aβ-induced neuroinflammation in both in vivo and in vitro AD models. Resveratrol can reduce the formation of Aβ fibrils and alleviate inflammation and oxidative stress, resulting in decreased Aβ and plaque levels in the brain. However, its low solubility, absorption efficiency, and BBB permeability result in poor bioavailability.[143] Li et al.[144] developed resveratrol-selenium-peptide nanocomposites (TGN-Res@SeNPs) with enhanced BBB transport efficiency. Administration of TGN-Res@SeNPs was observed to decrease Aβ aggregation, reduce Aβ-induced ROS, and down-regulate Aβ-induced neuroinflammation, thereby improving cognitive dysfunction in AD model mice. In a separate study, trehalose nanoparticles were shown to significantly improve anti-amyloidosis efficacy. Experiments conducted on cells and animal models demonstrated that trehalose nanoparticles alleviated cellular stress caused by extracellular Aβ oligomers and inhibited the aggregation of Aβ peptides in AD mice, offering a potential therapeutic strategy (Figure 13c).[145]

The complexity of AD, characterized by its multifactorial pathological processes, necessitates a comprehensive approach to improve treatment outcomes. The development of neuroprotective strategies that can target multiple aspects of the disease simultaneously is crucial. Recent advancements in nanotechnology have facilitated the creation of nanopreparations that combine multiple natural drugs, each with distinct mechanisms of action, to provide a comprehensive therapeutic effect against AD. Kim and his group have taken a significant step forward in this direction by developing nano delivery systems for two drugs, aiming to overcome the limitations associated with single-target therapies. They utilized berberine (BER) and rhein (RHE), which are primary bioactive compounds derived from Coptis chinensis and rhubarb, respectively. These compounds were synthesized into carrier-free nanoassemblies with intricate 3D porous framework crystal structures. This innovative approach demonstrated that

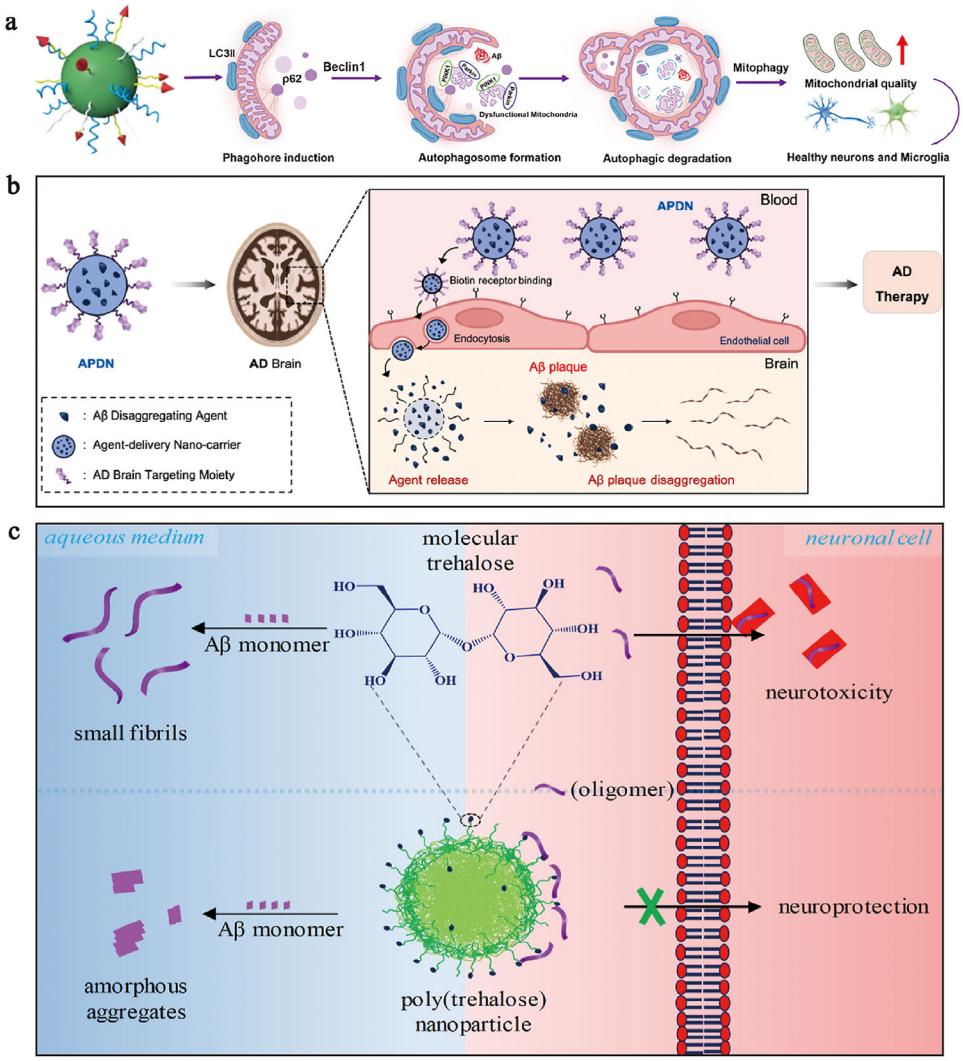

Figure 13. The mechanism of drug-delivery treatment of Alzheimer's disease. a) The mechanism of P@NB-mediated mitophagy. Reprinted with permission from ref. [138]. Copyright 2023 Wiley-VCH GmbH. b) Schematic illustration of amyloid-beta (Aβ) plaque disaggregating nano-platform. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [141]. Copyright 2023 Jaehoon Kim et al., published by Elsevier. c) Anti-Amyloidogenic Performance of Designed Poly(trehalose) Nanoparticle. Reprinted with permission from ref. [145]. Copyright 2023 American Chemical Society.

the BER-RHE assembly not only enhanced cholinesterase inhibition but also regulated Aβ aggregation, scavenging ROS and chelated metal ions, demonstrating superior anti-AD properties compared to the effects of the individual components.[107] In another approach to address the challenge of delivering therapeutic agents across the BBB, liposomes were employed as carriers for salidroside (SAL) and icariin (ICA), both known for their neuroprotective effects. The liposomes were surface-modified with angiopep-2 (Ang SAL/ICA Lip), a targeting molecule, to facilitate the penetration of the BBB by the nano drug delivery system. This modification enabled the liposomes to not only successfully cross the BBB but also to accumulate in the brain and be taken up by relevant cell types. As a result, the Ang-SAL/ICA-Lip system could reverse neuronal and synaptic damage, suppress neuroinflammation and oxidative stress, and enhance learning and cognitive functions.[146] Similarly, Wang et al. developed a brain-targeted anti-AD nanomedicine delivery system by co-loading icariin (ICA) and tanshinone IIA (TSIIA) onto long-circulating liposomes (Ang2-ICA/TSIIA) modified with animepep2 (Ang2). This system showed significant potential in inhibiting neuroinflammation and oxidative stress, reducing cell apoptosis, and improving cognitive functions in AD mice.[147]

Taken together, recent studies have explored various nanodelivery systems embedded with drugs in targeting the pathological processes of AD, such as Aβ accumulation, neuroinflammation, and oxidative stress. These systems have shown proficiency in crossing the BBB, reducing gastrointestinal side effects, increasing drug stability, and enhancing drug bioavailability. Using drug delivery strategies to efficiently deliver drugs that synchronize cholinesterase, Aβ aggregation and ROS clearance, the efficacy of nanodelivery is superior to that of single agents. ROS-responsive carriers that precisely release drugs in the focal area

Table 4. Drug-delivery strategies used in solving these challenges of drugs for the treatment of Parkinson's disease (PD).

ND	Drugs	Challenges	Drug-delivery strategies	Administration	Refs.
PD	Paeonia moutan	BBB and poor targeting	Paeonia moutan gold nanoparticles (PM-AuNPs)	Intravenous injection	[153]
PD	Cinnamomum verum	BBB	Gold nanoparticles (AuNPs)	Intravenous injection	[154]
PD	Ginkgolide B (GB)	BBB and poor targeting	Poly (ethylene glycol)-co-poly (ϵ-caprolactone) nanoparticles	Intravenous injection	[155]
PD	Paeoniflorin	BBB and poor targeting	Lactoferrin-black phosphorus nanosheets and near-infrared radiation	Intravenous injection	[156]
PD	Curcumin	Low stability and BBB	Analog-based nanoscavenger (NanoCA)	Intranasal delivery	[157]
PD	Curcumin	BBB and poor targeting	A 29 amino acid (RVG29)-modified red blood cell membrane (RBCm) to encapsulate curcumin nanocrystals	Intravenous injection	[158]
PD	Ferric ions and curcumin	Short half-life and BBB	Ultrasmall nanoscale coordination polymers (NCPs)	Intravenous injection	[159]
PD	Curcumin	BBB and poor targeting	Delivering curcumin by using a natural killer (NK) cell membrane-modified liposome-encapsulated curcumin	Subcutaneous administration near the local lymph nodes at the neck	[86]
PD	Puerarin	BBB and poor targeting	Lactoferrin-graphene oxide nanosheets	Intravenous injection	[160]
PD	Puerarin	BBB and poor targeting	Six-armed star-shaped poly(lactide-co-glycolide) nanoparticles	Intravenous injection	[161]
PD	Matrine	BBB	Black phosphorus nanosheets (BP) and near-infrared radiation	Intravenous injection	[162]
PD	Quercetin (QCT)	BBB and poor targeting	Mesoporous silica-encapsulated gold nanorods (MSNs-AuNRs) and near-infrared radiation	Intravenous injection	[64]
PD	Quercetin (QCT)	BBB and poor targeting	Prussian blue nanocomposite and near-infrared radiation	Intravenous injection	[163]

can enhance the clearance of localized Aβ deposition and reduce inflammation. The current strategy is focused on preclinical studies, and translation needs to overcome the challenges of dynamic BBB penetration, multi-target timing and synergistic multi-component delivery.

6.4. The Application of Drug-Delivery Strategies for Drug Therapy of Parkinson's Disease

Parkinson's disease (PD) is identified as a progressive neurodegenerative disorder characterized by motor symptoms, including resting tremors, bradykinesia, rigidity, and postural instability.[148] L-dopa remains the most efficacious treatment for the early motor symptoms of PD but does not offer a complete solution.[149] Its effectiveness is primarily observed in alleviating bradykinesia and rigidity; however, its impact on tremors is relatively limited, and it may not address balance issues and other symptoms.[150] Some natural drugs have been shown to protect the brain from the effects of PD neurodegeneration. For instance, vanillin possesses antioxidant, anti-inflammatory, and neuroprotective properties, demonstrating significant neuroprotection by enhancing antioxidant enzyme activities, reducing lipid peroxidation, and decreasing nitric oxide production.[151] Similarly, ferulic acid has been found to alleviate oxidative stress induced by rotenone, counteract free radicals through increased lipid peroxidation and antioxidant GSH levels, and reduce mitochondrial oxygen free radical generation, offering protection against oxidative damage in PD.[152] However, the clinical application of these drugs is limited by their structural instability, poor BBB permeability, short half-life, and low bioavailability, particularly when administered orally.

The utilization of drug-delivery strategy has significantly enhanced the therapeutic efficacy of these drugs in PD treatment. The drug-delivery strategies used in the drugs for the treatment of PD are systematically summarized (**Table 4**). Xue et al.[153] successfully synthesized gold nanoparticles using an extract of Paeonia moutan, applied in treating microglial BV2 cells and PD mice. The findings revealed that these gold nanoparticles significantly reduced inflammation in vitro and diminished neuroinflammation severity, leading to improved motor coordination in PD mice. In a separate investigation, the therapeutic potential of AuNPs synthesized from Cinnamomum for PD was assessed. These AuNPs were administered to a PD rat model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injection. The study outcomes demonstrated that AuNPs mitigated movement disorders and oxidative stress, and the activation of inflammatory cytokines in MPTP-induced PD rats.[154] Additionally, to overcome the limited bioavailability of ginkgolide B (GB) following oral administration, researchers developed poly (ethylene glycol)-co-poly(ϵ-caprolactone) (PEG-PCL) nanoparticles as a delivery vehicle for GB. When administered orally to rats, the GB-loaded nanoparticles (GB-NPs) attained higher concentrations of GB in the brain and blood than the free GB group. In a mouse model of PD, GB-NPs exhibited superior therapeutic effects and reduced toxicity relative to free GB.[155] Furthermore, Xiong et al.[156] engineered BP functionalized with the brain-targeting ligand lactoferrin (Lf) and loaded

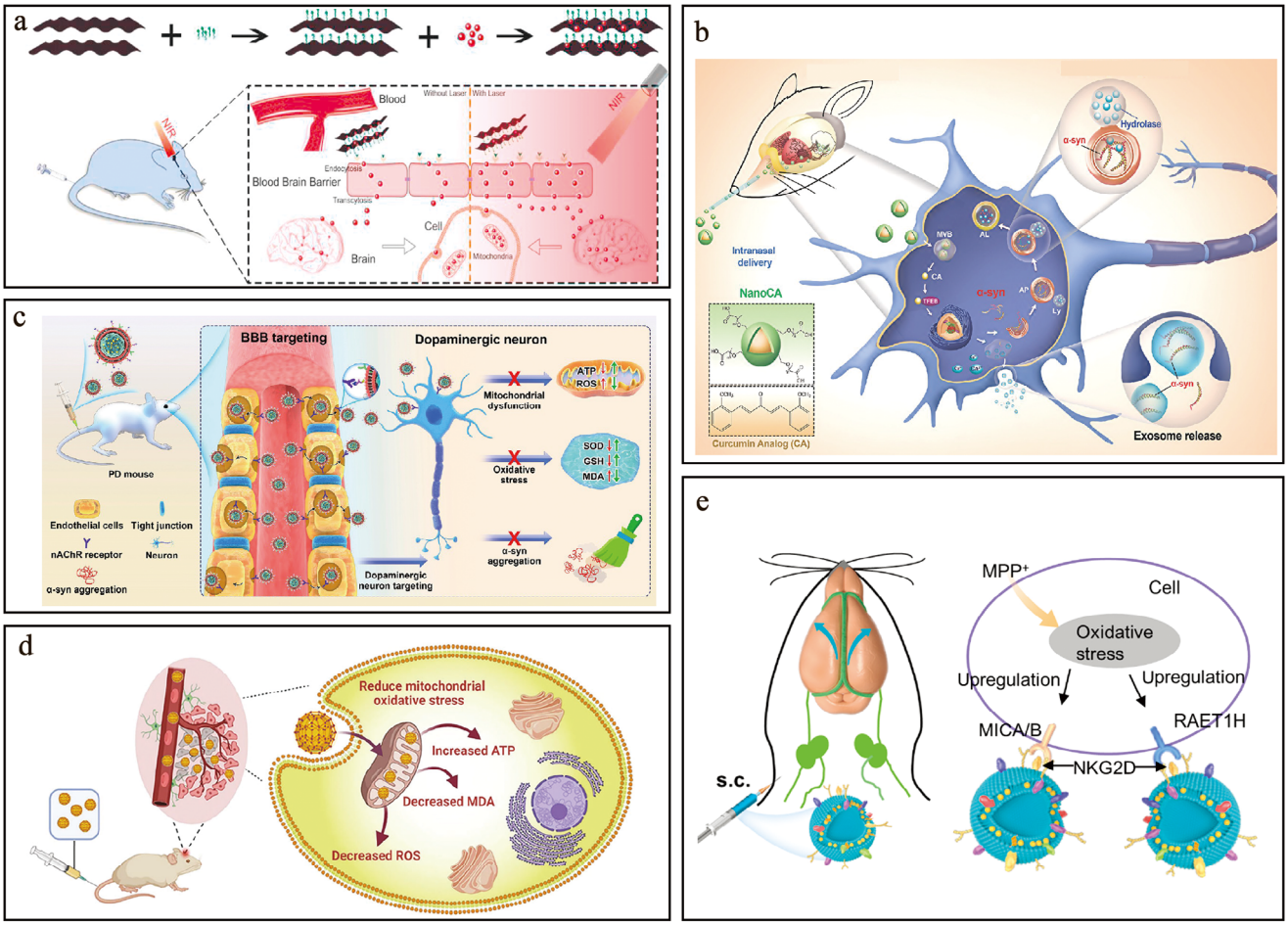

Figure 14. The mechanism of drug-delivery treatment of Parkinson's disease. a) The schematic overview of the development and use of the Lf-BP-Pae nano-platform for the treatment of PD. Reprinted with permission from ref. [156]. Copyright 2020 Elsevier Ltd. b) Design of self-assembled NanoCA for TFEB-regulated cellular clearance of α-syn in experimental models of PD. Reprinted with permission from ref. [157]. Copyright 2020 American Chemical Society. c) The application of RVG29-RBCm/Cur-NCs for PD therapy. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [158]. Copyright 2022 Yao Liu et al., published by American Chemical Society. d) Schematic illustration of the anti-Parkinsonian effects Fe-Cur NCPs. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [159]. Copyright 2022 Guowang Cheng et al., published by the American Association for the Advancement of Science (AAAS). e) Proposed mechanism of BLIPO-CUR against the Parkinson. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [86]. Copyright 2023 Jing Liu et al., published by the American Association for the Advancement of Science (AAAS).

with paeoniflorin (Pae), resulting in Lf-BP-Pae nanoparticles. Leveraging effective photothermal effects, Lf-BP-Pae successfully crossed the BBB, demonstrating efficacy in PD treatment (**Figure 14a**).

In the context of PD, characterized by the aggregation of α-synuclein in patients' brains, efforts have been directed toward the development of nano curcumin analogs (NanoCA), with capabilities to clear α-synuclein. The researchers showed that NanoCA promotes the nuclear translocation of transcription factor EB, thereby initiating autophagy and calcium-dependent exosome secretion, which facilitates the clearance of α-synuclein (Figure 14b).[157] Similarly, Liu et al.[158] engineered curcumin nanocrystals (Cur NCS) enveloped by red blood cell membranes that were further modified with rabies virus glycoprotein. This innovative approach enabled Cur NCS to evade the reticuloendothelial system (RES), extend its presence in the bloodstream, and enhance its penetration through the BBB following systemic administration. The results from this study confirmed the ability of Cur NCS to restore dopamine levels, mitigate α-synuclein aggregation, and rectify mitochondrial dysfunction in a PD mouse model (Figure 14c). In another innovative approach, understanding the critical role of excessive ROS accumulation and neuroinflammation in PD pathogenesis, Cheng et al.[159] synthesized ultra-small nanoscale polymers. These polymers were coordinated with ferric ions and integrated with the curcumin (Fe-Cur-NCP). This novel formulation was found to significantly extend blood circulation time and efficiently cross the BBB (Figure 14d), demonstrating its potential as a therapeutic agent in PD management. In a study utilizing a mouse model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, the application of Fe-Cur-NCP demonstrated encouraging outcomes in reducing oxidative stress, mitochondrial dysfunction, and inflammation within the midbrain and striatum regions, consequently alleviating symptoms associated with PD.

In another study, Liu et al.[86] utilized a strategy to deliver curcumin by using a natural killer (NK) cell membrane-modified liposome-encapsulated curcumin named BLIPO-CUR. BLIPO-CUR targets damaged neurons through membrane binding, scavenges ROS (Figure 14e), inhibits the aggregation of α-synuclein, and inhibits the diffusion of excess α-synuclein, thus improving the treatment of PD efficacy. Nonetheless, the deployment of puerarin (PUE), recognized for its anti-PD potential, faces challenges due to its limited water solubility, poor bioavailability, and inefficient BBB penetration. To overcome these obstacles, graphene oxide nanosheets encapsulating PUE were engineered, offering an enhanced drug loading capacity, modifiable surface functional groups, and excellent biocompatibility. The conducted in vitro and in vivo experiments underscored that this innovative brain-targeted drug delivery system proved to be an effective and safe approach for PD treatment.[160] In further research, six-armed star-shaped poly(lactide-co-glycolide) (6-s-PLGA) nanoparticles were used to encapsulate PUE, leading to notable improvements in intracellular internalization, permeability, and neuroprotective efficacy compared to the administration of PUE alone. In models of MPTP-induced neurotoxicity in mice, treatment with PUE-NPs was shown to mitigate behavioral impairments related to the disease and counteract the depletion of dopamine.[161]

The combination of nanomaterials and near-infrared irradiation has become an innovative approach for enhancing the permeability of the BBB, thus facilitating the delivery of natural drugs to the CNS. Javed et al.[162] created a nano-delivery system combining Matrine (MT) with polyethylene glycol-coated BP, aimed at reinstating homeostasis within the brain microenvironment for PD treatment. The photothermal effects induced by NIR irradiation allow these nanomedicines to traverse the BBB and penetrate the brain tissue. This method has shown promise in clearing excess ROS, diminishing neuroinflammation, reducing the aggregation of pathogenic proteins, and enhancing neurotransmitter function when applied in PD treatment. Liu et al.[64] developed a delivery system using mesoporous silica-encased gold nanorods (MSN AuNRs) loaded with Quercetin (QCT), a compound used in PD therapy, to improve BBB permeability through photothermal effects. The application of MSNs-AuNRs@QCT, followed by NIR-II irradiation, markedly ameliorated neurological deficits in mouse models of PD. Furthermore, another study employed imidazolate framework-coated Prussian blue nanocomposites (ZIF-8@PB) for encapsulating quercetin, facilitating the effective passage of ZIF-8@PB-QCT across the BBB. This method particularly targets mitochondrial dysfunction locations via the photothermal effect.[163]

The pathological core of PD involves abnormal aggregation of α-syn, loss of dopaminergic neurons and oxidative stress-neuroinflammatory cascade. Nano-delivery breaks through traditional drug limitations through biomimetic modification and pathology-responsive design to achieve efficient BBB penetration, resulting in reduced α-syn aggregation, targeted scavenging of ROS and improvement of mitochondrial function, and remission of dyskinesia in PD models. The current strategy focuses on preclinical studies, and its translation needs to address the dynamic clearance efficiency of α-syn, the clinical suitability of photothermal therapy, and the risk of immunogenicity of bionic vectors such as NK cell membranes.

6.5. The Application of Drug-Delivery Strategies for Drug Therapy of Epilepsy

Epilepsy is a serious CNS disorder characterized by abnormal, supersynchronized neuronal discharges in the brain. The manifestation of epileptic seizures is typified by recurrent, involuntary convulsions, loss of consciousness, and in extreme cases, even sudden death.[164] This imposes a significant social and psychological burden on patients and their families. The recurrent nature of seizure duration and its unpredictability necessitate the long-term administration of antiepileptic medications for all patients, with the aim of achieving seizure control.[165] Addressing the critical issue of enhancing the effective concentration of drugs in the epileptic focal area with the lowest possible drug dose while improving efficacy is paramount. The drug-delivery strategies used in the drugs for the treatment of epilepsy are systematically summarized (**Table 5**). Abnormal discharges, a hallmark of epilepsy, present a unique opportunity to engineer a responsive stimulatory drug delivery system. Zhou et al.[166] chose phenytoin (PHT) as a model drug and combined it with an electro-responsive moiety (sodium sulphonate, SS) and an epileptic foci-recognizing moiety (α-methyl-l-tryptophan, AMT). They designed a reactive oxygen/electrically dual-responsive nanogel, which was able to overcome the BBB hindrance and achieve targeted accumulation of epileptic foci. Subsequent stimulation by high concentrations of ROS, activation of the kynurenine pathway, and pathological factors associated with abnormal discharges achieved selective drug release from the lesion (**Figure 15a**). In another study, Zhong Chen's group[167] developed a novel nanomaterial that exhibits sensitivity to electric fields and possesses the capacity for targeted delivery to the brain in response to abnormal brain activity during epileptic seizures (Figure 15b). This material, composed of polypyrrole, polydopamine, and other components, is designed to respond to specific biological signals, demonstrating potential for targeted drug delivery applications. The nanomaterial introduces polydopamine into the polypyrrole conductive material, combines with the "peptide-NIR" co-targeting technology, and gives full play to the nanomaterial's drug loading, electric field response, and photo-thermal conversion properties to improve the targeting efficiency of the nano-delivery system. The experimental findings demonstrated that the nanomaterials, following the synergistic targeting effect of NIR and Angiopep-2, exhibited substantial accumulation in the temporal lobe region, a prevalent focal point of epilepsy. These nanomaterials demonstrated sensitivity to the electric field, resulting in drug release following electrical stimulation during epileptic seizures.

Most antiepileptic drugs face the problem of difficulty in passing the BBB after entering the circulatory system. The problem of BBB is well circumvented by using the natural kinship properties of biomimetic cell membranes. For example, to address the problems of insufficient BBB permeability and the short half-life of TC-DAPK6, a death-associated protein kinase 1 (DAPK1) inhibitor targeting epilepsy, Geng et al.[168] innovatively developed a macrophage membrane biomimetic nano-delivery system (MA@RT-HMSNs). Specifically, TC-DAPK6 and rhodamine B were encapsulated in hollow mesoporous silica nanocarriers (HMSNs) and coated with macrophage membranes. It was demonstrated that MA@RT-HMSNs were able to

Table 5. Drug-delivery strategies used in solving these challenges of drugs for the treatment of epilepsy (EP).

ND	Drugs	Challenges	Drug-delivery strategies	Administration	Refs.
EP	Phenytoin	BBB and poor targeting	Combined phenytoin with an electro-responsive moiety and an epileptic foci-recognizing moiety to achieve ROS/Electro dual-responsive	Intravenous injection	[166]
EP	Phenytoin	BBB and potential side effects	Combination of receptor-mediated transcytosis and BBB disruption–enabled transport induced by photothermal conversion of near-infrared light	intraperitoneally injection	[167]
EP	TC-DAPK6	BBB and short half-life	Macrophage membrane biomimetic nano-delivery system (MA@RT-HMSNs) encapsulating TC-DAPK6 and rhodamine B	Intravenous injection	[168]
EP	MnO2	Poor targeting	Bovine serum albumin as the nanocarrier to induce the formation of MnO2 nanocrystals through biomineralization with modified CD163 peptide	Intravenous injection	[169]
EP	Phenytoin	Significant toxicity in non-target organs and poor targeting	Hepatitis B virus core protein virus-like particle encapsulating phenytoin	Intravenous injection	[170]
EP	Inhibitory neuro-transmitters (GABA)	Adverse drug reactions and poor targeting	Reactive oxygen species (ROS)-induced in situ supramolecular assemblies	Intravenous injection	[171]

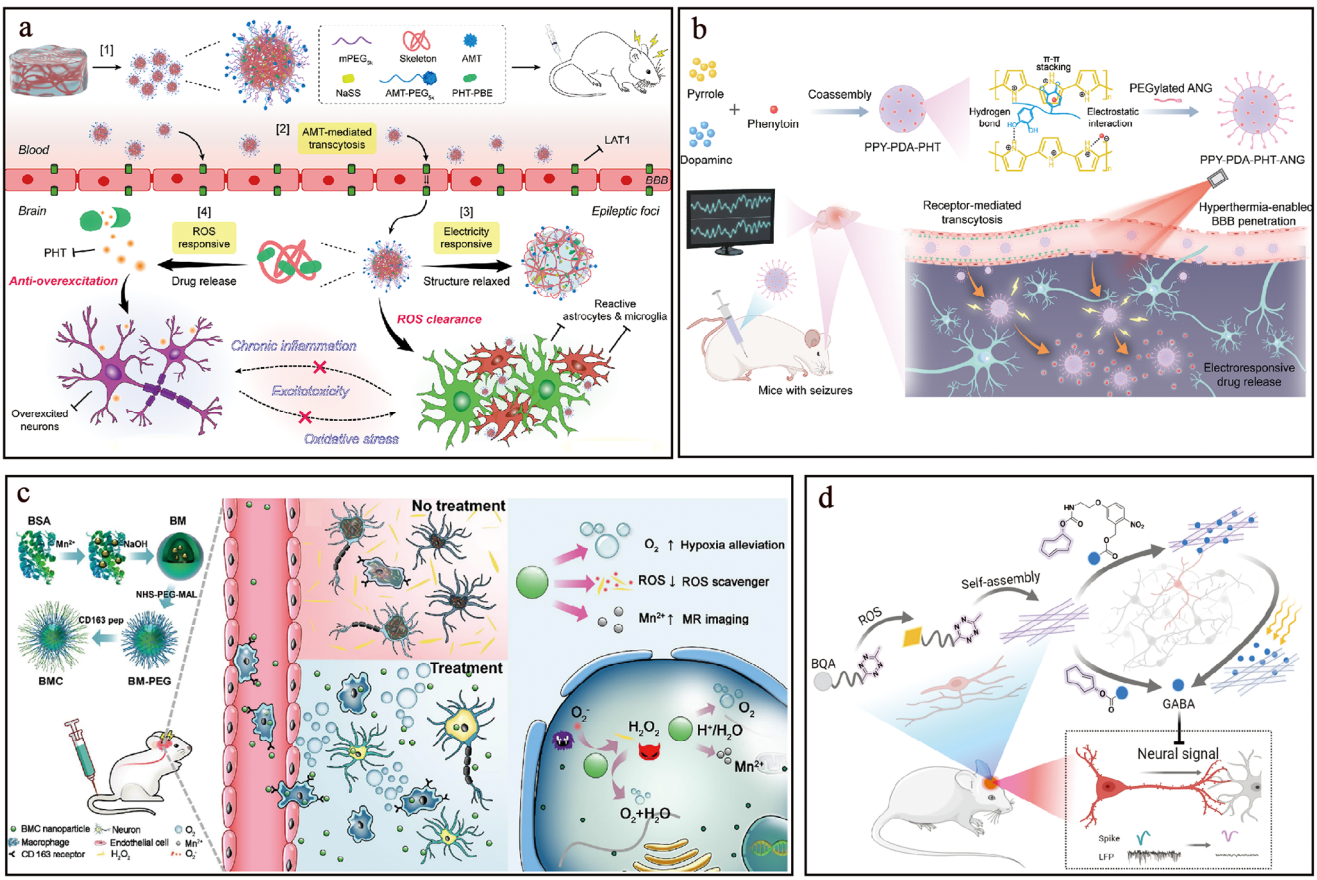

Figure 15. The mechanism of drug-delivery strategy for the therapy of epilepsy. a) Structure of the nanogel and its mechanism of targeting epileptic foci and ROS/electricity induced drug release. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [166]. Copyright 2022 Di Wu et al., published by the American Association for the Advancement of Science's (AAAS). b) Schematic illustration of the synthesis of electro-responsive brain-targeting nanoparticles and epilepsy therapy by intraperitoneal injection of PPY-PDA-PHT-ANG nanoparticles and NIR irradiation. Reprinted with permission from ref. [167]. Copyright 2023 American Chemical Society. c) Schematic Illustration shows BMC NPs hijacking of CD163 + macrophages for theranostics of epilepsy. Reprinted with permission from ref. [169]. Copyright 2023 Acta Materialia Inc. Published by Elsevier Ltd. d) ROS-instructed supramolecular assemblies guided the on-demand liberation of inhibitory neurotransmitters in the mice brain. Reprinted with permission from ref. [171]. Copyright 2024 Wiley-VCH GmbH.

efficiently cross the BBB and precisely deliver TC-DAPK6 to the inflammatory sites of epileptic foci. The macrophage membrane coating conferred higher stability and greater cellular uptake of MA@RT-HMSNs, significantly enhancing the bioavailability of TC-DAPK6. In addition, Lin et al.[169] used locally activated macrophages as carriers to deliver multifunctional nanoparticles to brain foci. CD163-positive macrophages in the epileptogenic zone were hijacked by the targeted albumin manganese dioxide nanoparticles, which were first used as a Trojan horse to efficiently penetrate the brain endothelial barrier and deliver the multifunctional nanomedicine to the epileptic foci. As magnetic resonance (MR)-responsive T1 contrast agents, multifunctional nanoparticles were used to accurately localize the epileptogenic zone with high sensitivity and specificity. At the same time, the catalytic nanoparticle synergistically scavenges ROS and modulates neuroinflammation, thereby protecting neurons in the brain (Figure 15c).

Most antiepileptic drugs (AEDs), including phenytoin as a sodium channel blocker, have access to other parts of the body such as the liver, kidneys, lungs, and bone marrow, and their clinical use is often limited due to the increased overdose, which usually causes significant toxicity to these organs, thereby exacerbating the deterioration of refractory epilepsy. In order to increase the specific targeting of PHT at the site of brain lesions and reduce the distribution to other tissues, Zhao et al.[170] constructed a protein nanocage for brain-targeted delivery of the antiepileptic drug PHT. A brain-targeting protein nanocage was designed and biosynthesized based on a Hepatitis B virus core protein virus-like particle (HBc VLP), and PHT was efficiently encapsulated inside the particle, which demonstrated excellent cross-BBB function and significant antiepileptic effect. Experiments showed that the drug-loaded protein nanocages have excellent cross-BBB function and significant antiepileptic effects, and can overcome the drug resistance problem of PHT. Similarly, to precisely deliver antiepileptic drugs (ASM) to epileptic foci without causing adverse drug reactions, Wu et al.[171] developed ROS-induced in situ supramolecular assemblies, which synergize bioorthogonal reactions to release inhibitory neurotransmitters (GABA) on demand. Under pathological conditions, tetrazine-containing precursors of the assemblies oxidize and selectively self-assemble within primary neurons and mouse brain (Figure 15d). The assemblies induce local aggregation of tetrazine in the CA3 region of the hippocampus, which results in the subsequent release of the inhibitory neurotransmitter in a bioorthogonal manner. In conclusion, the abnormal discharge and oxidative stress microenvironment of epilepsy drive the design of smart delivery systems. Drug delivery strategies for epilepsy can be designed with precise interventions of electrical response and oxidative stress microenvironment response. By developing a ROS/electrical dual-responsive delivery system, the precise release of drugs triggered by abnormal discharges leads to a more concentrated focal drug accumulation. Using photothermal synergistic strategies to modulate neuroinflammation by catalyzing ROS scavenging and oxygen generation, epileptic focus localization and neuroprotection can be achieved simultaneously. The current strategies are mostly in the preclinical stage, and the translation needs to optimize the clinical appropriateness of the electrical stimulation parameters, the bionic membrane scale-up preparation process, and the dynamic monitoring system of drug resistance.

6.6. The Application of Drug-Delivery Strategies for Drug Therapy of Glioblastoma

Glioblastoma (GBM) is a highly aggressive brain tumor that exhibits therapeutic resistance, stemming from its interaction with the surrounding microenvironment and barriers such as the BBB.[172] Despite the development of peptides, chemotherapeutic agents, and other drugs, the progress in clinical trials is slow. The immunosuppressive microenvironment of the tumor, the presence of the BBB, and the inherent instability of GBM vaccines have been identified as key factors contributing to this slow progress, which collectively impede improved therapeutic efficacy.[173] Gboxin, an inhibitor of oxidative phosphorylation, has been shown to specifically inhibit the growth of GBM through inhibition of the activity of the F0F1ATP synthase complex V. However, the anti-GBM effect and further clinical applications of Gboxin are limited by poor blood circulation, BBB, nonspecific GBM tissue/cellular uptake, and insufficient accumulation at the GBM site. Zou et al.[174] Constructed a ROS-responsive nanoparticle in cancer cell-mitochondrial heterodimeric membrane camouflage for the targeted delivery of Gboxin (**Figure 16a**), which effectively prolonged Gboxin's blood circulation time, increased the permeability of the BBB and enhanced its accumulation at the tumor site, ultimately achieving efficient GBM treatment.

To address the fact that the BBB severely hinders the entry of therapeutic agents into the brain as well as the non-targeted distribution of drugs that often produce side effects on susceptible brain tissues, Chi et al.[175] proposed a hybrid cellular membrane camouflage strategy to prepare therapeutic nanocomposites consisting of brain metastatic breast cancer (HMBC) cellular membranes and glioma cellular membranes via a simple membrane fusion pathway. By encapsulating hybrid cell membranes (HMs) on drug-carrying nanoparticles, the obtained biomimetic therapeutic agents (called HMGINPs) inherited both satisfactory BBB penetration and homologous glioma-targeting ability from the two source cells (Figure 16b). The HMGINPs showed good biocompatibility and better therapeutic efficacy for early-stage gliomas. In another study, Fan et al.[176] reported that a microglia membrane-encapsulated biomimetic nanoparticle (BM@MnP-BSA-aPD-1) was applied to targeted drug delivery in an in situ glioma model, which remodeled the immunosuppressive tumor microenvironment (TME) through a combination of multiple pathways (PTT, STING pathway activation, PD-1/PD-L1 blockade), induced a cascade of local and systemic anti-tumor immune effect, effectively inhibiting tumor growth and significantly prolonging survival, providing a promising new strategy for anti-GBM immunotherapy.

Temozolomide (TMZ) is a first-line drug that has been approved by the FDA for the clinical treatment of glioma. It has been shown to effectively reduce the invasion of tumor cells. However, it has a short half-life, requires long-term, high-dose administration, and is prone to myelosuppression, drug resistance, and other side effects. To address these problems, Chen et al.[177] developed an effective strategy using hollow manganese dioxide (HMnO2) as a carrier material, adding polydopamine (PDA) to enhance stability and brain targeting, grafting RAP-12 peptide on the outer layer to further improve stability and brain targeting, and combining co-targeting technology and the

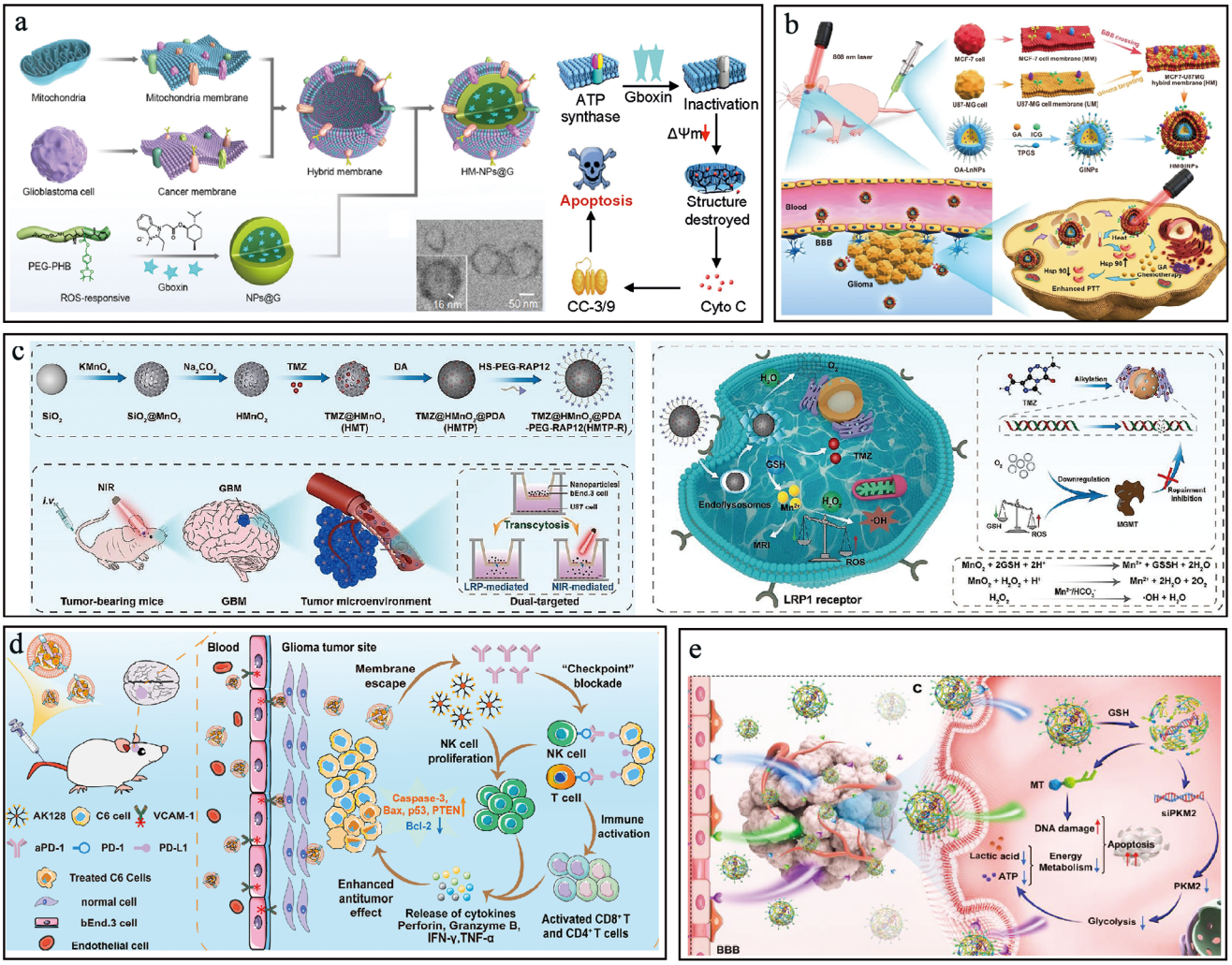

Figure 16. The mechanism of drug-delivery treatment of glioblastoma. a) Fabrication of cancer cell-mitochondria hybrid membrane camouflaged Gboxin encapsulated ROS-responsive polymeric nanoparticles (HMNPs@G). Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [174]. Copyright 2023 Yan Zou et al., published Springer Nature. b) Schematic illustration of the fabrication of HMGINPs and the mechanism of BBB penetrating, glioma targeting, and enhanced photothermal therapy. Reprinted with permission from ref. [175]. Copyright 2023 Wiley-VCH GmbH. c) Schematic illustration of the preparation of dual-targeted nanoparticles and the dual-targeted strategy of LRP- and NIR-mediated transcytosis. Adapted with permission under a Creative Commons Attribution 4.0 International (CC BY 4.0) License from ref. [177]. Copyright 2024 Xiaojie Chen et al., published Springer Nature. d) Schematic illustration of AK128-aPD1@M1m NCs for synergistic regulation of NK cells and T cells and enhanced glioma immunotherapy. Reprinted with permission from ref. [178]. Copyright 2024 American Chemical Society. e) Schematic illustration of ApoE-MT/siPKM2 NC preparation and suppression of GBM by responsive drug release after efficient BBB penetration. Reprinted with permission from ref. [179]. Copyright 2024 Wiley-VCH GmbH.

use of tumor microenvironment to alleviate the adverse effects caused by TMZ, enhance its targeting ability and improve its therapeutic efficacy in the treatment of gliomas. The dual-targeting tumor microenvironment responsive nanoformulation was constructed for the multi-effective synergistic diagnosis and treatment of gliomas (Figure 16c), with the high expression of glutathione (GSH). Under the action of GSH and hydrogen peroxide (H2O2), HMnO2 was degraded to produce oxygen (O2), which alleviated the hypoxic microenvironment of the tumors. While GSH was consumed to enhance hemodynamic therapy (CDT), manganese ions (Mn2+) released can be used for MRI of the brain and further promote the release of TMZ, exerting a synergistic therapeutic effect of chemotherapy and CDT.

Inspired by the activity of autoimmune cells for obtaining ideal tumor immunotherapy, Peng et al.[178] developed a nanomedicinal formulation based on a phospho-dendrimer-like macromolecule (AK128)/cell programmed death protein 1 antibody (aPD1) nanocomplex (NC), which was camouflaged by M1-type macrophage membranes (M1m) to enhance the immunotherapy of glioma in situ. The constructed AK128-aPD1@M1m NC had and good stability and cytocompatibility and the modified M1m had $\alpha 4$ and $\beta 1$ integrins, which enabled the NC to penetrate the BBB and co-deliver AK128 and aPD1 with intrinsic immunomodulatory activity to in situ gliomas, prolonging the blood circulation time. Studies results showed that the phospho-dendritic molecule AK128 promotes the proliferation of natural killer (NK)

Table 6. Drug-delivery strategies used in solving these challenges of drugs for the treatment of glioblastoma (GBM).

ND	Drugs	Challenges	Drug-delivery strategies	Administration	Refs.
GBM	Gboxin	Poor targeting	ROS-responsive nanoparticle in cancer cell-mitochondrial heterodimeric membrane camouflage for the targeted delivery of Gboxin	Intravenous injection	[174]
GBM	Hybrid cell membranes	BBB and poor targeting	Hybrid cellular membrane camouflage strategy to prepare therapeutic nanocomposites consisting of brain metastatic breast cancer (HMBC) cellular membranes and glioma cellular membranes via a simple membrane fusion pathway	Intravenous injection	[175]
GBM	PD-1/PD-L1 blockade	Serious systemic cytotoxicity and BBB	Microglia membrane-encapsulated biomimetic nanoparticle (BM@MnP-BSA-aPD-1)	Intravenous injection	[176]
GBM	Temozolomide (TMZ)	Short half-life	A strategy using hollow manganese dioxide (HMnO2) as a carrier material to alleviate the adverse effects caused by TMZ, and adding polydopamine (PDA) and grafting RAP-12 peptide to enhance stability and brain targeting	Intravenous injection	[177]
GBM	Phospho-dendrimer-like macromolecule (AK128)/cell programmed death protein 1 antibody (aPD1)	Short half-life and poor targeting	Nanomedicinal formulation based on a phospho-dendrimer-like macromolecule (AK128)/cell programmed death protein 1 antibody (aPD1) nanocomplex (NC), which was camouflaged by M1-type macrophage membranes (M1m) to enhance the immunotherapy of glioma in situ	Intravenous injection	[178]
GBM	Temozolomide (TMZ)	Short half-life and poor targeting	novel TMZ nanocapsule (ApoE-MT/siPKM2 NC) for the combined delivery of pyruvate kinase M2 siRNA (siPKM2) and TMZ	Intravenous injection	[179]

cells in peripheral blood mononuclear cells, whereas delivered aPD1 restores cytotoxic T-cells and NK cells via immune checkpoint blockade (ICB), thus promoting apoptosis of tumor cells (Figure 16d).

Aerobic glycolysis, the predominant energy supply mode of GBM multiforme (GBM), impacts the efficacy of radiotherapy while ensuring the rapid proliferation of GBM. In order to effectively inhibit aerobic glycolysis and improve drug delivery efficiency and sensitivity, Rutong Yu's group[179] designed and prepared a novel TMZ nanocapsule (ApoE-MT/siPKM2 NC) for the combined delivery of pyruvate kinase M2 siRNA (siPKM2) and TMZ. This drug delivery platform employs siPKM2 as the core component and methacrylate-TMZ (MT) as the shell component, thereby achieving the inhibition of glioma energy metabolism while enhancing the killing effect of TMZ (Figure 16e). By modifying apolipoprotein E (ApoE), the dual targeting of the BBB and GBM is achieved in a "two birds with one stone" manner. The nanocapsules are designed to be cleaved in a targeted manner by GSH-responsive cross-linkers containing disulfide bonds, releasing MT and siPKM2 in the high GSH environment of glioma cells. In summary, various drug-delivery strategies enhance the efficacy and reduce side effects of anti-GBM drugs. The drug-delivery strategies used in the drugs for the treatment of GBM are systematically summarized (**Table 6**). The treatment of GBM is limited by poor BBB penetration, tumor immunosuppressive microenvironment and chemotherapy resistance. Nano-delivery enhances efficacy and reduces toxicity through bionic design and pathologic response mechanisms. On the one hand, the use of GBM cell membrane-modified nanocarriers can be endowed with natural homologous targeting and immune escape ability, which can significantly enhance the accumulation efficiency of drugs in the tumor site, and realize synergistic drug-immune therapy. Based on the high GSH, hypoxia and acidic characteristics of the GBM microenvironment, the design of smart-responsive nanoplatforms can precisely release drugs and regulate metabolism. For example, GSH-triggered oxygen-producing nanoparticles can not only alleviate tumor hypoxia to enhance radiotherapy sensitivity, but also achieve chemotherapy-chemokinetics synergistic treatment by releasing chemotherapeutic drugs and free radical generation. The current strategy focuses on preclinical research, and the translation needs to break through the bottleneck of safety and dynamic metabolic microenvironment adaptability of bionic membrane immune checkpoint therapy.

7. Conclusion and Future Perspectives

Neurological disorders (ND) remain therapeutic challenges due to BBB impermeability, off-target effects, and multifactorial pathogenesis.[180] In order to address the challenge of drug delivery to the BBB, there are several strategies that can be employed. The initial strategy entails the utilization of physical stimulation to facilitate the opening of the BBB, employing techniques such as non-invasive electrical stimulation, light stimulation, and ultrasound. The second strategy is the utilization of nanocarriers, which can be modified with chemical technology and biotechnology to facilitate the traversal of the BBB. However, a significant challenge remains in the development of nanocarriers with high drug loading rates.

Another significant challenge to neurologic therapy is the targeted delivery of therapeutic medications to specific locations within the brain. The benefits of targeted drug delivery include reducing the required drug dosage, improving bioavailability at the targeted sites, and minimizing peripheral side effects. Taking a targeted approach can make use of modification of the drug by recognizing proteins expressed specifically by the target tissues and cells loaded on the surface of the drug carrier, such as transferrin. Another approach is to design responsive drugs, such as

ROS, pH response, electrical response, ultrasound response, and magnetic response, to promote the release of drugs only when the corresponding pathological factors are produced specifically at the pathological site, while no drugs are released at the non-targeted part, thus circumventing the damage of the drugs to the normal tissues to the greatest extent possible. In addition, the majority of existing studies have employed a single pathological factor response. However, numerous ND are characterized by the presence of multiple pathological processes. Consequently, a unifactorial analysis is insufficient to fully elucidate the underlying mechanisms and inform precision treatment strategies. The development of composite intervention strategies that encompass multiple responses represents a promising avenue for future research.

Furthermore, the multifactorial pathogenesis of ND demands multi-target approaches. Utilizing the concept of cocktail therapy, nanomaterials offer the opportunity to combine various drugs, each with different effects, to achieve a synergistic therapeutic impact. However, due to the diverse structures and properties of these drugs, a single nanocarrier may not meet the delivery requirements for each unique drug. Therefore, it is imperative to investigate efficacious and stable nanocarriers for diverse compounds and devise tailored and appropriate nanocarriers for drug delivery.

In summary, different drug-delivery strategies may be employed to address the various challenges associated with drug entry into the nervous system. Each of these strategies possesses a distinct set of advantages. The combination of multiple strategies can be employed when confronted with particular neurological issues, thereby circumventing the issues associated with drug entry into the body, including poor BBB penetration, poor targeting, and toxic side effects. Several directions deserve further exploration in future research. The first is to further optimize nanocarriers, such as developing nanocarrier particles with smaller size, higher drug loading capacity, better biocompatibility and targeting to achieve efficient drug delivery in the nervous system. Second, cells such as neural stem cells and macrophages could be utilized as drug carriers to deliver drugs to specific parts of the nervous system. Through surface modification of specific ligands or antibodies, the drug carriers can specifically bind to nerve cells or lesion sites to improve drug targeting. The third is to develop an intelligent drug delivery system, which can adjust the amount of drug release in real time according to the patient's physiological data, and realize the on-demand release of drugs. Converging these innovations will bridge the translational gap between preclinical efficacy and clinical viability for ND therapeutics.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

Alzheimer's disease, blood-brain barrier, drug delivery, epilepsy, glioblastoma, Parkinson's disease, stroke

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