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Nanomaterial-Based Blood-Brain-Barrier (BBB) Crossing Strategies

Jinbing Xie[a,b], **Zheyu Shen**[c,*], **Yasutaka Anraku**[b], **Kazunori Kataoka**[b,d,*], **Xiaoyuan Chen**[c,*]

[a]Jiangsu Key Laboratory of Molecular Imaging and Functional Imaging, Department of Radiology, Zhongda Hospital, Medical School of Southeast University, Nanjing 210009, China.

[b]Innovation Center of NanoMedicine, Kawasaki Institute of Industrial Promotion, 3-25-14, Tonomachi, Kawasaki-ku, Kawasaki 210-0821, Japan.

[c]Laboratory of Molecular Imaging and Nanomedicine, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Bethesda, Maryland 20892, United States.

[d]Policy Alternatives Research Institute, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

Abstract

Increasing attention has been paid to the diseases of central nervous system (CNS). The penetration efficiency of most CNS drugs into the brain parenchyma is rather limited due to the existence of blood-brain barrier (BBB). Thus, BBB crossing for drug delivery to CNS remains a significant challenge in the development of neurological therapeutics. Because of the advantageous properties (*e.g.*, relatively high drug loading content, controllable drug release, excellent passive and active targeting, good stability, biodegradability, biocompatibility, and low toxicity), nanomaterials with BBB-crossability have been widely developed for the treatment of CNS diseases. This review summarizes the current understanding of the physiological structure of BBB, and provides various nanomaterial-based BBB-crossing strategies for brain delivery of theranostic agents, including intranasal delivery, temporary disruption of BBB, local delivery, cell penetrating peptide (CPP) mediated BBB-crossing, receptor mediated BBB-crossing, shuttle peptide mediated BBB-crossing, and cells mediated BBB-crossing. Clinicians, biologists, material scientists and chemists are expected to be interested in this review.

Keywords

blood-brain barrier (BBB); central nervous system (CNS); nanomaterials; drug delivery systems

* shawn.chen@nih.gov; zheyu.shen@nih.gov; kataoka@ifi.u-tokyo.ac.jp.

Conflicts of interest

There are no conflicts to declare.

1. Introduction

CNS diseases including Alzheimer's disease and Parkinson's disease, strokes and brain cancers are the world's leading causes of disability, and thus have been attracting more and more attentions [1–5]. However, very few drugs are successful for the treatment of the CNS diseases and the therapeutic efficacy is greatly limited by many factors [6], among which ineffective transportation of drugs across the BBB is the biggest challenge [7,8]. The efficiency of drug transportation across the BBB greatly depends on the properties of molecular size, hydrophilicity, dissociation degree, and so on [9,10]. Up to now, it was reported that most small-molecule drugs and almost all macromolecular drugs (*e.g.*, recombinant proteins, therapeutic antibodies, and nucleic acids) cannot cross the BBB [9,11]. Thus, the development of drug delivery systems that can effectively transport therapeutic agents into the CNS is of critical importance in the treatment of CNS diseases.

For decades, nanomaterials have received increasing attentions in drug and gene delivery. Many nanomaterials, including inorganic nanoparticles, polymeric nanoparticles, micelles, liposomes, and nanofibers, have been designed as theranostics showing unparalleled advanatges, such as relatively high drug loading content, controllable drug release, excellent passive and active targeting, good stability, biodegradability, biocompatibility, and low toxicity [14–19]. Recently, nanomaterials have been considered as versatile drug transportation systems across BBB, which can deliver the loaded theranostics agents into the CNS. In addition, approaches avoiding uptake by the reticuloendothelial system (RES) enable drug-loaded nanomaterials to have a prolonged blood circulation, which significantly improves the BBB-crossing opportunities of nanomaterials resulting in a relatively high drug accumulation in the brain parenchyma. All these advantageous properties enable nanomaterials to play significant roles in drug delivery across the BBB. Based on the nanotechnologies, many strategies were widely exploited for the transportation of theronostic agents across the BBB, for example, receptor-mediated transcytosis, disruption of BBB with mechanical or ultrasound, shutter peptide mediated BBB-crossing, and intranasal delivery of nanomaterials. In addition, many characteristic properties of nanomaterials (*e.g.*, particle size, composition, hydrophilicity, hydrophobicity, dissociation degree, and surface charge) could affect the transportation ability across the BBB, which provides broad space for researchers to develop more promising strategies for nanomaterial-based BBB crossing.

In this review, we will provide the latest progress in nanomaterial-based BBB crossing strategies for the imaging and/or treatment of CNS diseases.

2. BBB and CNS diseases

2.1 BBB

BBB is a physical and metabolic barrier that limits transportation between the blood and neural tissues. It plays an important role in keeping the stability of physiological environment of brain tissues and protecting the CNS from infraction by harmful agents or microorganisms in the blood. The inner layer of BBB is mainly composed of endothelial cells on brain capillary walls and tight junctions, which hinder the transportation of cargos

through the paracellular passage between the adjacent endothelial cells in the inner layer (Figure 1) [8,20]. Additionally, peripheral cells and the matrix lie in the middle layer (*i.e.*, basement membrane). The outer layer has the extracellular matrix and astrocytes [21,22]. Besides the physical barrier, BBB also includes a biochemical barrier with a lot of transporters and enzymes. The high resistance between the brain microvessel endothelial cells (BMVECs) constitutes electrochemical basis, and the efflux system on the cell membrane forms physiological basis of the BBB [23]. It is worth noting that although tight connection forms by the strong cohesive system in the BBB, small molecules (*e.g.*, glucose, and hydrophobic molecules with molecular weight smaller than 500 Da) and certain cells (*e.g.*, monocytes, macrophages and neutrophils) could be selectively transported into the brain.

Delivery of most therapeutic agents into the brain should pass through the endothelial cells. The paracellular passage between endothelial cells could be used for the transportation of ions and solutes crossing BBB, which is called paracellular pathway. The transcellular passage on the endothelial cells could be used for transportation of many cargos across BBB, which is named transcellular pathway, or transcytosis. The transportation balance between paracellular and transcellular pathways could keep the healthy environment of brain. The transcellular pathway usually allows passive diffusion of small lipophilic molecules (< 500 Da), transportation of gas molecules (*e.g.*, carbon dioxide) depending on specific receptors, and transportation of hydrophilic polar molecules (*e.g.*, glucose, proteins and peptides) depending on specific transporters (*e.g.*, glucose transporter-1 (GLUT-1), choline transporters, and large-amino acid transporter 1 (LAT1), or specific receptors for insulin, transferrin, lipoprotein, and interleukin-13) (Figure 2). These highly selective transporter-mediated transportation and receptor-mediated transcytosis could be applied to design nanomaterials for BBB-crossing. Caveolae is another pathway for the transportation of molecules in or out the brain which depends on a formed vesicle around the molecules *via* cellular invagination. Recently, the transcellular pathway has been widely explored and many strategies have been designed for the transportation of therapeutic agents into the brain tissue (Figure 2). However, the BBB-crossing efficiency may be reduced by the active efflux pumps of ATP-binding cassette transporters (ABCs) for the transportation of some neurotoxic lipid-soluble molecules or other therapeutic drugs into the blood. The efflux pumps could be well downregulated by the cytosolic and extracellular-membrane enzymes in the endothelial cells. The efflux system plays very important roles in maintaining the normal physiological environment of the brain *via* excretion of heterologous substances and toxic metabolites [24–26].

The physiological environment of brain and the exchange between CNS and peripheral system are mostly dependent on the morphological structure and features of the BBB. On the one hand, the morphological structure of BBB allows it to play an essential role to protect the brain. On the other hand, the physiological barrier of BBB prevents the transportation of therapeutic agents into the brain. The above-mentioned paracellular and transcellular pathways can be used for efficient delivery of therapeutic agents into the CNS.

2.2 CNS diseases

The patient number of CNS diseases has been increasing in the world while the development of therapeutics is greatly limited because of the BBB. Many strategies based on nanomaterials have been developed to overcome the BBB for the treatment of CNS diseases. Herein, the BBB roles and the targeting efficacy of nanomaterials towards the CNS diseases (*i.e.*, Alzheimer's disease, multiple sclerosis, Stroke, Parkinson's disease, and glioblastoma) are presented.

2.2.1 Alzheimer's disease—Alzheimer's disease (AD) is an early stage neurodegenerative disorder with the most prevalent form of dementia. Patients' social and behavioral skills are greatly affected by the decreased cognitive ability. Several possible mechanisms concerning the cerebrovascular dysfunctions of Alzheimer's disease have been reported, such as BBB disruption, impaired glucose transport, decreased cerebral blood flow, and increased capillary tortuosity with altered rheology [27]. Some of these proposed mechanisms could enhance the pathological effects of the others, but they are not mutually exclusive of one another. In addition, some mechanisms were considered to sustain pathological processes, and some mechanisms were thought to take responsibility for initiating events that probably lead to the Alzheimer's disease.

BBB plays a fundamental role in Alzheimer's disease. According to the neurovascular hypothesis, decreased BBB clearance of Aβ is one of the main reasons that may induce increased amyloid burden in the brain and the corresponding Alzheimer's disease [28]. Decreased levels of the brain-to-blood efflux transporters of LRP1 [29] and P-gp [30], increased oxidation of LRP1 [31], and a decreased level of P-gp activity [32] were found in the endothelial cells of AD patients. Inflammation-induced increase in pericyte uptake of Aβ may be a mechanism for explaining the loss of pericytes in AD, due to the toxicity of Aβ to pericytes [33,34]. Reduced production of CSF leads to the decrease of bulk flow. Although the reason why the bulk flow is decreased in aging and AD is still unclear, it has been realized that inflammation can result in decrease of the bulk flow and disruption of the BBB. Thus, based on this mechanism, many therapeutic strategies were developed through using the BBB disruption to deliver drugs, blocking the neuroinflammation, and targeting the astrocytic aquaporin production.

2.2.2 Multiple sclerosis—Multiple sclerosis (MS) is a neuroinflammatory disease with demyelination and CNS invasion by immune cells, such as macrophages and lymphocytes. Although the predisposing factor and precipitating event are still unknown, MS is thought to be self-perpetuating after its establishment because the CNS invasion by immune cells is a cause of neuroinflammation. The MS animal model with BBB dysfunctions in experimental allergic encephalopathy has characteristics of BBB disruption, invasion of immune cells and altered cytokine transportation. Peripheral signals across BBB may induce microglia and astrocytes secreting substances, which act on brain endothelial cells (BECs) and subsequently increase the invasion of immune cells. The clinical characteristics of multiple sclerosis are mainly induced by the BBB penetration of immune cells. The α4 integrin is a surface protein of immune cells, through which immune cells can bind to vascular cell adhesion molecule 1 (VCAM1) on BECs and its blocking can inhibit the CNS invasion of

immune cells [35]. In addition, there are many steps for the CNS invasion of immune cells. Briefly: 1) a process referred to tethering and rolling; 2) leukocyte activation *via* chemokine stimulation of G-protein linked receptors; 3) tight adhesion of leukocyte to the BECs, and subsequent matrix metalloproteinase (MMPs) expression resulting in the basement membrane degradation; and 4) migration of leukocytes across CNS endothelium driven by chemokine-chemokine receptor interactions. Each step includes a set of BBB receptors that could provide multiple targets for amending the CNS invasion of immune cells [36]. For example, during the BBB crossing process of immune cells into the CNS, the degradation of the sub-endothelial basement membrane was mediated by proteolytic enzymes of MMPs. The quantum dot complexed with MMP-9 siRNA has been used to reduce the expression of MMP-9 in brain and subsequently inhibit the migleukocyte immune cell invasion into the CNS [37]. In addition, pMHC-coated iron oxide nanoparticles were also applied for the inhibition of MMP-9 and inflammation [38]. NAC loaded polyamidoamine dendrimers were developed to suppress the neuroinflammation and increase motor function in the cerebral palsy [39].

2.2.3 Stroke—Stroke can lead to a long-term disability status in adulthood affecting about 0.8 million people per year worldwide. The brain lacks blood supply during the episode of stroke due to a bleeding vessel of hemorrhagic stroke or vessel occlusion of ischemic stroke induced by a blood clot [40,41]. The deprivation of oxygen and nutrients in both hemorrhagic stroke and ischemic stroke leads to brain cell death, dysfunction of neurons and ultimate death of patient. During the episode of ischemic stroke, short opening time from minutes to hours and a following refractory interval may happen to the BBB, after which, BBB may undergo an reopening time from hours to days [42–44]. To reduce the cerebral injury *via* blood re-supply, and the endothelium activation, recruitment of leukocyte, production of cytokine and ROS, and the formation of edema may lead to the reopening of BBB [45].

Drug delivery for the stroke should consider the compromised tight junctions, and the initial and late opening of the BBB. Taking advantage of the BBB-opening time window and the receptors expressed on the luminal side of endothelial cells may be helpful for the BBB-crossing of nanoparticles. Thus, BBB itself could be a promising target for improving the transportation of drug into the ischemic brain.

2.2.4 Parkinson's disease—About 10 million people in the world suffer from the Parkinson's disease (PD). In PD patients, selective degeneration of dopaminergic neurons in substantia nigra leads to the depletion of dopamine in striatum. There are Lewy bodies in neurons which are composed of α-synuclein and protein inclusions [46]. The correlation between the progressive BBB damage and the pathology course has been indicated by the difference of the albumin ratios in PD patients' brain and control group [47]. People also found that there are some associations between cerebral blood flow deficiencies and vascular alterations or the loss of BBB integrity in striatum and substantia nigra of PD patients [48,49]. An increasing expression of VEGF has a correlation to more blood vessels growing in the periphery of damaged dopaminergic neurons in monkeys' substantia nigra [50].

Furthermore, injection of VEGF into the substantia nigra of rats could induce the disruption of BBB and a consequent dopaminergic neurons loss as well as a strong inflammation [51].

Inflammation of astrocytes, infiltration of T-leukocytes, and microgliosis in the brain of PD patients and rat models are related to the permeability of BBB and loss of dopaminergic neurons [52,53]. A lot of pro-inflammatory cytokines of TNF-α, IL-1β and mterferon-γ are released, and ROS and NO are greatly produced in microglia and astrocytes of PD patients, which are thought to be correlated with BBB impairment [53,54]. In addition, α-synuclein deposition in brain was considered as one of the causes of PD. It was found that the P-gp downregulation may induce α-synuclein deposition [55] and the increase of BBB dysfunction in lipopolysaccharide administrated mice [56]. Increased amount of metals (*e.g.*, manganese and iron) were found in lesioned regions of animal models and PD patients' brain [57]. Increasing lactoferrin receptor in substantia nigra dopaminergic neurons of parkinson's disease patients and animal models may be related to the neuronal iron uptake, resulting in the degeneration of dopaminergic neurons. In addition, increased level of lactoferrin receptor in the blood-brain vasculature was considered to be associated with BBB dysfunction in PD [58,59]. Thus, understanding whether the hallmarks of PD pathogenesis could trigger vascular impairment is very important for the development of the most effective therapeutics of PD.

2.2.5 Brain tumors—Brain tumors, a heterogeneous group of primary and metastatic neoplasms in CNS, have a super poor prognosis and very low survival rate of patients [60]. Glioblastoma (GB) has been thought to be the most frequent primary brain tumor, which is most aggressive and lethal in people [61]. It's a great challenge for GB therapy due to the complex and heterogeneous molecular biology, which leads to different prognosis of patients subjected to the same treatment strategy [62,63].

Primary brain tumors (PBT) are the malignancies that originate and reside within the brain. Metastatic brain tumors arise from a primary cancer such as lung cancer, breast cancer, colorectal cancer, renal cell cancer or melanomas outside of the CNS [64]. It was reported that about 70% of brain metastases result from breast and lung cancers [65,66]. The lethality of high-grade brain tumors stems from the invasiveness and the resistance to radiotherapy and chemotherapy [67,68]. Many anticancer drugs have adverse feature of poor hydrophilicity, high hazardous and toxic side effects to healthy organs [69–71]. Nanotechnology has been widely developed and nanomaterials hold great promise for the targeted delivery of anticancer drugs, such as paclitaxel and doxorubicin [72–74]. However, the existence of BBB is a great impediment for the delivery of drug-loaded nanoparticles from the blood circulation system to CNS as well as brain tumor site. Thus, transportation of anticancer agents loaded nanomaterials across BBB is still the biggest challenge in the treatment of brain tumors. The properties and the design stratagies of nanoparticles (NPs) mostly depend on cancer type, development stage, and tissue location [75–77]. Modification of functional biomolecules on the surface of nanomaterials for anticancer drug delivery may contribute to precise targeting and high efficiency treatment with low or none side effects [78–80]. Payload delivery efficiency could be improved by the ligand and receptor-mediated endocytosis.

Increasing cytotoxicity and decreasing volume of xenografts were obtained in treating nonsmall lung cancer *via* the interaction between aptamers and molecular targets using aptamer-conjugated NPs compared with non-targeted NPs [81,82]. Accordingly, the application of NPs in the treatment of brain tumor, particularly glioblastoma, has been addressed in various preclinical and clinical studies [83,84]. PEG modified hexadecyl cyanoacrylates NPs have been studied for evaluation of the tumor targeting using a rat gilosarcoma model, and abundant accumulation of NPs is the tumor site was found [85,86].

3. Nanomaterials for BBB-crossing

Nanomaterials have been widely developed to transport therapeutic drugs through the BBB due to their obvious advantageous features, such as relatively high drug loading content, enhanced stability, prolonged blood circulation time, controlled drug release and targeting effect. The size, zeta potential and hydrophilicity of nanomaterials play important roles in their fate *in vivo*. In addition, nanomaterials can be engineered with surface modifications to tune and control various functional properties (*e.g.*, enhancing the tumor accumulation *via* modification of targeting ligands, and increasing the blood circulation time *via* modification of polymers to shield the targeting ligands in blood and expose them in tumors) [87,88]. Herein, the nanomaterial-based BBB crossing mechanisms, study methods for BBB transportability of nanomaterials, and nanomaterial-based BBB crossing strategies, were presented and discussed.

3.1 Study methods for BBB transportability of nanomaterials

Development of various study methods is very important to understand the BBB transportability and fundantional mechanisms of nanomaterials. The study methods at different levels have their corresponding roles and characteristics. For example, the *in vitro* BBB models could help perform high-throughput screenings with low cost, and the *in vivo* models could offer further evaluation for clinical translation. In this section, we briefly summarize and discuss the study methods for the BBB transportability of nanomaterials (Figure 3).

3.1.1 In vitro BBB models—*In vitro* BBB models were developed for studying the uptake, transportation mechanism, bio-distribution and cytotoxicity of nanomaterials. The *in vitro* BBB models offer opportunity for performing high-throughput screenings, which facilitate not only manipulating BBB-affected parameters (*e.g.*, glycemia, hypoxia, and toxins), but also reducing animal testing cost. Most of the *in vitro* BBB models are based on brain endothelial cells (BECs) isolated from mouse, rat, or human [89–91]. Besides, stem cells are also used for the *in vitro* BBB models [92,93]. Some of the *in vitro* BBB models are mono-cultures of BECs with two-dimensions or three-dimensions, or co-cultures of BECs with astrocytes, BECs with pericytes, BECs with pericytes and astrocytes. Cho *et al.* developed a microfluidic platform for mimicking BBB dynamics in stroke based on rat BECs showing increase of reactive oxygen species (ROS) levels and decrease of ZO-1 expression upon oxygen and glucose deprivation [94]. Recently, *in vitro* BBB models for reproducing aspects of AD and PD BBB properties were developed. Co-culture of rat BECs isolated from PD animals and rat astroglial cells showed signals of BBB dysfunction of P-gp

overexpression and lower transelectrical resistance, which is similar to that of *in vivo* 6-OHDA PD model and has been applied for drug delivery studies in PD [95]. An *in vitro* BBB model based on the co-culture of porcine BECs and a human neuroblastoma cell line transfetced with a luciferase reporter vector coupled to an ADAM10-promoter, which is crucial for avoiding toxic cleavage of amyloid precursor protein (APP), was used for predicting drug delivery across the BBB in AD. Besides, this *in vitro* BBB model can be further tuned to study drug delivery in other pathologies [96]. *In vitro* BBB models can also be used to screen nanomaterials *via* evaluation of their BBB transportability. For example, an *in vitro* BBB model has been developed for screening nanomaterials with various sizes and surface functionalizations, so that their physicochemical characteristics could be defined for the design of nanomaterials with high BBB transportability [97].

3.1.2 Model organisms in BBB study—Recently, model organisms in BBB study have been considered as an intermediate step to link *in vitro* co-culture models and *in vivo* rodent BBB studies, and sometimes they were thought to be a potential replacement for the *in vitro* BBB models. The most attractive application of these model organisms is to screen compound libraries with functional read-out that is based on toxicity, behavior or pharmacodynamics in one whole disease-like model organism. Zebra fish and drosophila have been developed for BBB study and drug screening. The drosophila brain contains a single epithelial layer, hemolymph, and subperineurial glia, which form a passive diffusion barrier through chemically tight septate junction complexes. The barrier feature of efflux chemicals through Pgp-like mechanisms in this model organism allows for screening of efflux pump substrates and their toxicity [98]. However, the obvious differences between the cellular and structural features of drosophila BBB and that of mammalian species BBB greatly limits the application of this model organism (*i.e.*, drosophila) in further BBB study.

The BBB of zebra fish is similar to mammalian species in anatomical and function features [99], and it may reproduce most organizational characteristics of BBB, fluids of choroid plexus and ventricular system, and the transporters [100–102]. Besides being transparent during larval stage that is suitable for pharmacokinetic tracking of agents injected from the peripheral or center, zebra fish has a high sequence similarity of many BBB transporters and BBB receptors to that of human [101]. In addition, some assays of zebra fish behavior have been applied for preclinical study of specific CNS targets and BBB permeability drugs [103]. Recently, this model organism has been used for *in vivo* screening of BBB permeability of indoline derivatives [104]. A lot of CNS ‘disease-like’ models have been made by manipulating genes of zebra fish [103]. Besides, SiO_2 nanoparticles and cadmium telluride (CdTe) quantum dots have been used to study the neurotoxicity and behavior in zebra fish [105,106]. This model organism (*i.e.*, zebra fish) still needs to be rigorously investigated to determine whether the findings from zebra fish can predict the drug efficacy in human.

3.1.3 In vivo BBB models—*In vivo* BBB models are very important for providing more insights into drug delivery across the BBB due to their irreplaceable clinical relevance and higher complexity. Although many *in vitro* BBB models and model organisms have been developed, none of them can reproduce the complete BBB in animal body with the

complexity of the integrated neurovascular unit. Thus, it's urgently needed to develop *in vivo* BBB models for selection of potential therapeutic agents that are very likely to be used in the clinic.

Study of nanomaterials BBB transportability based on *in vivo* BBB models needs quantification and imaging techniques to monitor nanomaterials delivery into the CNS. For example, gold nanoparticles are available for quantification and monitoring by ICP-MS and TEM, and have been widely applied to screen drugs crossing the BBB [107,108]. Nanoparticles can be found in brain capillaries of rats and mice within half an hour after *i.v.* injection [107,108]. This phenomenon is consistent with the result of *in vitro* work that nanoparticles can be relatively rapidly taken up by endothelial cells through endocytosis pathway [109]. At 1.0 h post administration, nanoparticles are observed to cross the BBB (Figure 4) [110]. The transportation kinetics of nanoparticles can be affected by the particle size and the chemistry on particle surface.

3.2 Nanomaterial-based BBB crossing strategies

Many drug delivery methods have been developed and a variety of drugs have been successfully transported into the brain across the BBB based on nanomaterials. Herein, the nanomaterial-based BBB crossing strategies are presented and discussed.

3.2.1 Intranasal delivery—Intranasal administration is an effective and noninvasive approach for delivering drugs into the brain overcoming the barrier of administration from the parenteral route. Utilizing intranasal delivery approach, therapeutic agents could be effectively transported to the CNS across the olfactory mucosa, and along the connective tissue around the olfactory nerve bundle or axons of olfactory neurons, and thus bypass the BBB (Figure 5) [111]. The intranasal delivery may effectively avoid the first pass metabolism of liver, decrease drug accumulation at non-targeting tissues, and therefore minimize the systemic side effects. In addition, intranasal delivery has been one of the popular methods in drug delivery due to its many advantages, such as relatively rapid adsorption, rapid onset, non-invasiveness, non-destructiveness, and easy operation (Figure 5) [112,113].

Up to date, a lot of therapeutic drugs including proteins, peptides, and small molecules have been delivered into the brain *via* intranasal route [7]. For example, Fonseca *et al.* designed a muco-adhesive system of amphiphilic methacrylic copolymer-functionalized poly(epsilon-caprolactone) nanocapsules for delivering olanzapine through intranasal route [114]. In this work, it was demonstrated that these nanocarriers may interact with nasal mucosa, by which the retention of olanzapine on the nasal mucosa increased. Furthermore, it was found that administration of nanocapsules ended up with more accumulation of olanzapine in the brain of rats than that of free drug. Of note is that the integrity of nasal mucosa can be broken by repeated administration of the olanzapine-encapsulated nanocarrier, which means that this therapeutic drug-encapsulated nanocapsule is a muco-adhesive system for delivering drugs into CNS through nose-to-brain pathway [114]. It must be pointed out that the surface area of olfactory region of the nasal epithelium is very limited with only about 5% in human, although abundant in rodent reaching up to 50%. Thus, the therapeutic drug level that has

been obtained in mice with the intranasal delivery is one order of magnitude over-estimated when extrapolated into human brain. Kozlovskaya *et al.* studied the brain drug delivery efficiency of different administration types of intranasal delivery systems according to the available quantitative data [115]. It was found that the differences of drug delivery efficiency between various intranasal delivery nanomaterials are significant, which almost has no correlation with the physicochemical properties of the loaded drugs. Although hydrogel- and nanomaterial-based intranasal delivery systems themself contribute limited advantages for the drug delivery to the CNS, conjugation of some special functional reagents on the surface of hydrogels or nanomaterials (*e.g.*, mucoadhesive compounds, absorption enhancers, and/or targeting ligands) can help increase the drug delivery efficiency into the CNS through the intranasal route [115]. Recently, drug delivery *via* nasal-brain pathway has been studied extensively and applied as an alternative approach for the vaccine administration (Figure 5) [116,117]. However, the existence of significant differences in drug delivery efficiency between various nasal routes indicates that further studies of more effective intranasal delivery strategies are still required [111,118,119].

3.2.2 Temporary Disruption of BBB—Temporary disruption of BBB has been widely studied as a prevalent approach for delivering drugs into the CNS from circulatory system [120]. The developed BBB disruption methods mainly include osmotic disruption, ultrasound disruption, and magnetic disruption.

Osmotic disruption: Agents like mannitol, fructose, milk amide, urea, and glycerol may produce a high osmotic pressure resulting in temporary BBB opening. For example, mannitol can be used for opening the BBB temporarily, and its efficiency is highly dependent on the mannitol concentration, injection speed, and the retention time after administration (Figure 6) [121,122]. The mechanism of mannitol induced BBB opening is that the dehydration of the vascular endothelial cells leads to the shrinking and disruption of the tight junctions, which can result in subsequent transportation of drugs into the brain. However, irreversible CNS damage may be induced by the increased BBB permeability, which may allow the delivery of macromolecular substances into CNS across BBB and then result in the neuropathological changes, such as myelin disintegration [123,124]. Besides, BBB disruption allows some toxic and harmful agents to enter the CNS, which may result in a change of the CNS normal functions [125].

Ultrasound disruption: Recently, ultrasound-based techniques for reversible BBB opening have been widely studied. The ultrasound-based techniques depend on the energy of acoustically activated microbubbles to provide a transient and reversible permeabilization of vascular endothelium, promoting transportation of desried molecules into the CNS across the BBB [126]. Alkins *et al.* applied focused ultrasound with injection of microbubbles to enhance the uptake of ^{10}B-enriched L-4-boronophenylalanine-fructose (BPA-f) [127]. For this purpose, a 558 kHz transducer, which can produce a pulsed ultrasound, and microbubbles, were used to disrupt the BBB in gliosarcoma model rats. As a result, the ^{10}B accumulation in the gliosarcoma in the ultrasound-microbubbles group was 1.63-fold higher than that of the control group. Furthermore, Aryal *et al.* found that the delivery efficiency of liposomal doxorubicin could be improved by using the focused ultrasound technique, which

induced an increased median survival of 100% and 72% compared with the control groups with non-treatment and DOX only, respectively [128].

Magnetic disruption: The transportation rates of nanoparticle ferrofluids could be greatly improved by magnetic gradients. Heat can be generated when magnetic nanoparticles are exposed in alternating magnetic fields. So, the magnetic nanoparticles can become a local heat source with alternating magnetic field [129,130]. Weinberg *et al.* found that magnetic gradients could greatly improve the transportability of magnetic nanoparticles into the brain olfactory bulb crossing the cribriform plate [131]. In addition, the BBB transportability of therapeutic magnetic nanoparticles can be further improved *via* combination with the focused ultrasound. The synergistical delivery technology could be applied in both healthy and pathological brains, which greatly improved the brain accumulation of the drug-loaded magnetic nanoparticles (Figure 6 and Figure 7) [132,133]. The BBB permeation was studied by using ultra-small superparamagnetic iron oxide (USPIO) nanoparticles-loaded poly(butyl cyanoacrylate)-based microbubbles (MB) [133]. The USPIO-MB was first magnetically guided to the target tissue under an external magnetic field, and the local disruption of the targeted BBB was then obtained by the transcranial ultrasound pulse exposure. In addition, the application of alternating magnetic field combined with osmotic disruption can also improve the BBB tranportability of iron oxide nanoparticles (IONPs) [134].

3.2.3 Local delivery—Local delivery of drugs into the CNS has been studied for a long time [135,136]. To date, a lot of strategies with local delivery of different therapeutic agents have been developed. The initial work of local nanodrug delivery into the CNS focused on implanting biodegradable polymer wafers with loaded drug, which had a controlled drug release fashion for a prolonged period of time and resulted in an improved therapeutic effect [137]. Although an enhanced dose of drug could be delivered to the tumor resection, the limited penetration of the drug released from the implants over the tumor margin greatly limited the therapeutic efficacy [138]. Recently, much attention has been paid to the liposomal nanoparticles for local delivery of drug into CNS [139,140]. Besides, the bulk fluid flow from convection enhanced delivery (CED), which depends on the external pressure gradient as provided by a syringe pump, can promote the continuous infusion of drug-loaded nanoparticles into the brain [141]. This CED approach can greatly enhance the brain accumulation of therapeutic agents over a large volume (Figure 8) [142–144].

Previously, polymer microspheres of PLGA, poly(methylidene malonate) (PMM), poly(epsilon-caprolactone), and chitosan, were applied for local delivery of a range of therapeutic agents into the CNS without surgery, including phenytoin, paclitaxel, mitoxantrone, imatinib, and nerve growth factor, *etc* [145,146]. However, the brain distribution of these microparticles is limited due to their relatively large size (usually over 1 μm in diameter). Recently, nanoparticles, especially those less than 100 nm in size were used for drug delivery instead of huge microparticles, and these drug-loaded nanoparticles can be transported by CED [147,148]. It was reported that the intracranial tumor model could be effectively treated with locally delivered camptothecin-loaded PLGA nanoparticles *via* CED [149]. A higher volume distribution was achieved by using CED than the traditional infusion method [144,148,149]. Some clinical trials have shown the feasibility of intracranial delivery

of free drug molecules with CED approach [150]. It is reasonable to predict the clinical benefit of CED of nanoformulas as well with less off target effects and limited systemic toxicity as compared to systemic delivery.

3.2.4 Cell penetrating peptide (CPP) mediated BBB crossing—CPP, a type of short peptides characterized as amphipathic and cationic, has strong ability to help the conjugated therapeutic agents or biomaterials rapidly cross the cell membranes [151–154]. There are mainly two types of cationic CPPs, *i.e.*, antimicrobial sequences, and chimeric peptides [155]. Although the cell membrane transportation mechanism of CPPs is still not clear, the binding of cationic charges in CPPs to the brain endothelial cell membrane surfaces *via* electrostatic interactions is helpful for the transportation of CPPs-modified nanomaterials across the BBB. Previously, a direct penetrating process without energy dependence or endocytosis was proposed to be the mechanism for the transmembrane penetration of CPPs [156]. However, this mechanism was challenged by recent research works, according to which endocytosis especially macropinocytosis could be the main pathway of CPP-mediated internalization of cellular membrane [156]. It was reported that the transportation efficiency of nanomaterials into the brain can be greatly enhanced after conjugation of CPPs. For example, a remarkable brain delivery efficiency of 6% was obtained by using CPP modified PLGA nanoparticles *via* the nasal route, which was only 1.36% for non-CPP modification nanoparticles as reported by Lu *et al* [157]. Wen *et al.* prepared magnetic poly (D,L-lactide-co-glycolide) (PLGA)/lipid nanoparticles (MPLs) with PLGA, L-a-phosphatidylethanolamine (DOPE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-amino (polyethylene glycol) (DSPE-PEG-NH2) and magnetic nanoparticles (NPs). The trans-activating transcriptor (TAT) peptide was then conjugated onto the surface of MPLs to produce TAT-MPLs, which can target the brain based on the magnetic guidance and TAT penetration. It was found that QDs-loaded TAT-MPLs were efficiently delivered into the BECs as evidenced by the high fluorescence intensity in the cytoplasm and cell nucleus. The conjugation of TAT on MPLs significantly improved the cellular uptake of delivered drugs in bEnd.3 cells by enhancing the cell membrane penetration, offering great potential in designing effective BBB crossing drug delivery systems (Figure 9) [158].

3.2.5 Receptor mediated BBB crossing—Delivery of many endogenous macromolecules into the brain depends on the receptor-mediated transcytosis pathway. The interactions between ligands and corresponding receptors expressed on the surface of BECs promote the formation of corpuscles *via* endocytosis pathway, and then the formed corpuscles release the ligands with crossing the BBB into CNS *via* exocytosis to play their biofunctions. This process is so-called receptor-mediated transcytosis for BBB-crossing. Therefore, various ligands of receptors could be conjugated onto the nanomaterials to improve the delivery of loaded therapeutic agents into the CNS through the corresponding receptor mediated BBB-crossing pathway, which is a promising BBB-crossing strategy in biomedicine field.

Recently, advancements in biomedical sciences and technological tools have led to a better and deeper understanding of the pathophysiology of CNS diseases. This has improved our

knowledge regarding the upregulation of several receptors that can be used for the delivery of drugs across the BBB. Several typical receptor-mediated BBB crossing strategies are summarized and discussed in the following sections.

Transferrin receptors: The brain transportation pathway based on the transferrin receptor (TfR), which is abundantly expressed in the brain capillary endothelial cells (BECs), has been widely studied for brain delivery of drug-loaded nanomaterials [159]. It was reported that the accumulation of anti-TfR antibodies in brain is much higher than that of non-specific immunoglobulins [160]. However, some studies indicated that although the anti-TfR antibodies can be transported through BECs, it is difficult to obtain a high therapeutic concentration in the brain for drugs with conjugation of anti-TfR antibodies through the TfR-mediated transportation pathway. That's because the drug-receptor complex may be degraded in the endosome or lysosome of BECs (*i.e.*, intracellular degradation of the drugs) [161–163].

In order to solve the problem of endosomal degradation, many approaches have been developed. For example, Clark and Davis developed an approach that can tune the antibody-binding strength with TfR to mimic endogenous transferrin, which leads to high brain uptake of the antibodies [164–166]. Another approach introduced an acid-cleavable linker between the transferrin ligand and gold nanoparticles, which resulted in escape of the nanoparticles from endosomal degradation and thus greatly improved the transportation efficiency of the nanoparticles into the CNS (Figure 10) [167]. An 8-fold increase of dopamine distribution in the brain tissue of PD model rats was achieved with administration of dopamine-loaded PEGylated liposomes with conjugation of thiolated anti-TfR monoclonal antibody through the linker lipid (DSPE-PEG-Maleimide) [168]. In addition, the TfR-mediated transportation with T7 peptide has also been successfully used for the efficient delivery of small interfering RNA (siRNA) to down-regulate EGFR protein expression in glioma [169]. More accumulation of T7-LPC/siRNA NPs was observed in brain tumor than the non-targeted NPs of LPC/siRNA NPs. In addition, longer survival period accompanying with the higher downregulation of EGFR expression in tumor was obtained in mice with an intracranial U87 glioma administration of T7-LPC/siEGFR NPs as compared with the mice treated with LPC/siEGFR NPs.

Lactoferrin receptors: Lactoferrin (LF) is a cationic iron-binding glycoprotein. It is involved in host defense against infection and severe inflammation, and accumulates in the brain during neurodegenerative disorders [170]. The LF receptor has been demonstrated to exist at BECs of the BBB and has been shown to be involved in LF-receptor-mediated transcytosis through the BBB *in vitro* and *in vivo* [171]. Recently, it was further demonstrated that LF is a promising brain-targeting ligand due to its higher uptake efficiency compared to transferrin and OX-26 (an anti-transferrin-receptor antibody) [172]. LF was also used as a brain-targeting ligand for desgining brain drug nanocarriers [173,174].

Shen *et al.* exploited Fenton-reaction-acceleratable magnetic nanoparticles, *i.e.*, cisplatin (CDDP) loaded Fe_3O_4/Gd_2O_3 hybrid nanoparticles with conjugation of LF and RGD dimer (RGD2) (FeGd-HN@Pt@LF/RGD2), for MRI-guided high efficiency ferroptosis therapy (FT) of orthotopic brain tumors [175]. As shown in Figure 11, FeGd-HN@Pt@LF/RGD2

can transport across the BBB because of its exceedingly small size (6.6 nm) and LF-receptor-mediated transcytosis, and can be internalized into brain tumor cells due to the $\alpha_v\beta_3$ integrin receptor mediated endocytosis. The released Fe^{2+} and Fe^{3+} in brain tumor cells as two of the three reactants can directly accelerate the Fenton reaction. The released CDDP in brain tumor cells can induce generation of H_2O_2 that can also accelerate Fenton reaction as another reactant. The acceleration of Fenton reaction can generate abundant reactive oxygen species (ROS) to kill brain tumor cells (*i.e.*, FT of brain tumors).

Folate receptors: Folate is a low molecular weight pterin-based vitamin. The significant overexpression of folate receptors (FR) on both BBB and glioma cells, while low expression in normal brain tissues, inspires people to develop effective folate-conjugated nanocarriers for delivery of drugs into brain tumors. For example, a kind of micelle-like nanoparticles conjugated with folic acid *via* redox-sensitive bonds were developed for the delivery of cytochrome c to brain tumors [176]. In addition, delivery of anti-cancer agent using folic acid modified elongated cellulose nanocrystals showed obvious FR-mediated transportation according to the studies of cellular binding/uptake in brain tumor cells of both human and rat [177]. Recently, folate and N-(trimethoxysilylpropyl) ethylene diamine triacetic acid (TETT) conjugated MnO nanoparticles (MnO-TETT-FA) have been developed as a tumor-specific MRI contrast agent for glioma imaging [178]. MR images indicated that the tumor accumulation of MnO-TETT-FA nanoparticles was higher than that of MnO-TETT nanoparticles. In addition, FR-targeting systems have been widely studied as promising therapeutics of glioma [179,180].

Lipoprotein receptor-related protein: The low-density lipoprotein receptor-related proteins (LRPs), such as LRP1 and LRP2, are highly expressed in BBB and their corresponding ligands may be used for the BBB-crossing of nanomaterials. The LRP ligands are also applied for the targeting of brain tumors due to the high expression of LRPs in glioma cells. For example, the aptamer-functionalized PEG-PLGA nanoparticles with conjugation of LRP1 ligand angiopep-2 showed BBB crossing ability through the receptor-mediated transcytosis, and efficacy in clinical trials for the glioma patients [181]. The PF127-modified water-dispersible poly(acrylicacid)-bound iron oxide nanoparticles with surface conjugation of angiopep-2 was used for the brain delivery and showed high BBB-crossing efficiency due to both the LRP receptor and the clathrin-receptor mediated transportation.

Scavenger receptors: Although scavenger receptors (SRs) were originally studied as a kind of transmembrane glycoprotein playing role in scavenging modified lipoprotein, such as acetylated and oxidized low-density lipoprotein [182], they have shown the ability of recognizing and binding to a broad spectrum of ligands, including modified, and unmodified host-derived molecules or even microbial components. These receptors could mediate the cellular uptake of both oxidized lipoproteins and microbes. Out of many types of SRs, SRA1 and SRB1 have high expression on the brain capillary endothelial cells (BCECs) [183,184]. The peptide vector of PepFect 32 with modification of angiopep-2 ligand has been used for delivery of plasmid DNA with forming PF32/pDNA nanocomplexes. It was proved that the

nanocomplexes could be transported across BECs *via* scavenger receptor class A and B (SCARA3, SCARA5, and SR-BI)-mediated transcytosis [185].

Interleukin-13 receptor a2 (IL-13Ra2): IL-13Ra2, a member of the family of IL-13 cytokine receptors, could bind IL13 with very high affinity. However, it has no known function as a signal mediator [186,187]. IL-13Ra2 plays a role of internalizing IL13 after binding [188]. IL-13Rα2 is highly expressed in a variety of cancers, including malignant gliomas. IL-13 has shown remarkable ability of BBB-crossing after combination with other functional molecules, such as cell penetrating peptides (CPPs). It was reported that an peptide of Pep-1 (CGEMGWVRC) could help transport drugs into the brain across BBB *via* the IL-13Ra2-mediated transcytosis approach [189]. Furthermore, the ligand IL-13 containing copolymer nanoparticles with modification of Pep-1 was developed for the delivery of paclitaxel. An obvious enhancement of paclitaxel delivery efficiency to glioma has been obtained in the intracranial glioma model mice with administration of the Pep-1-modified copolymer nanoparticles [190]. In addition, conjugation of two peptides (*i.e.*, IL-13 peptide with function of binding to IL-13Ra2, and RGD peptide with function of binding to $\alpha_v\beta_3$ integrin receptor) produced dual targeting polymeric nanoparticles, which further improved tumor delivery due to the clathrin-mediated endocytosis [91].

Insulin receptors: Insulin receptors, one of the tyrosine kinase linked receptors, could mediate the transportation of insulin across the BBB [191]. However, the endogenous ligand insulin has not been used as a vector due to the following two reasons: 1) the degradation of insulin in the blood stream is rapid with a short blood half-life of 10 min; 2) the hypoglycemia may be induced by breaking the balance of natural insulin [192]. Antibodies that can recognize insulin receptors have been applied to develop BBB-targeting vectors. For example, by using an amphiphilic diblock copolymer of poly(dimethylsiloxane)-block-poly(2-methyl-2-oxazoline) formed polymersomes with conjugation of anti-human insulin receptor antibody (clone 83–14), specific uptake by hCMEC/D3 cell was obtained [193]. Anti-insulin receptor monoclonal antibody (29B4) was conjugated onto the loperamide-loaded human serum albumin (HSA) nanoparticles. The HSA nanoparticles showed significant antinociceptive effects in the tail-flick test in ICR (CD-1) mice, which indicated that this antibody conjugation to HSA nanoparticles could help deliver loperamide across the BBB [104].

Glutamate receptors: Type 1 metabotropic glutamate receptors is a G-protein coupled receptor, which is related to many diseases including drug addiction, epilepsy, anxiety, and pain. There are several classes of receptors that bind glutamate, *e.g.*, DL-α-amino-3-hydroxy-5-methylisoxazole propionic acid and kainic acid receptors, metabotropic receptor, and N-methyl-D-aspartate receptors (NMDAR)) [194]. Through activation of NMDAR, glutamate was used to induce the disruption of human cerebral endothelial barrier [195]. It was reported that the neurotransmitter glutamate plays an important role in modulating the early barrier permeability *in vivo*. Increased vascular permeability in the rat cerebral cortex induced by the recurrent seizures and the associated excessive glutamate release *via* activation of NMDAR were observed *via* an intravital microscope [196].

Glucose receptors: Glucose, the main energy source in the brain, has been widely studied in drug delivery due to the remarkably higher expression level of glucose transporter-1 (GLUT1) in BCECs compared with many other receptors and transporters [197]. Recently, Anraku *et al.* reported a strategy based on exploiting the rapid glycemic increase after fasting which enables remarkably enhanced transport of nanoparticles across the BBB through GLUT1 [198]. Besides, GLUT1 is also overexpressed in some tumors, potentiating drug delivery and tumor therapy. Glucose ligand conjugated micelles were studied *in vitro* and *in vivo* against GLUT1-high human squamous cell carcinoma of the head and neck OSC-19 cells, and GLUT1-low human glioblastoma-astrocytoma U87MG cells. High tumor accumulation accompanied with high efficacy against the tumors was observed in OSC-19 tumors [199]. Shao *et al.* designed a reduction-sensitive nanoformula and gained a high effect of anti-glioma and anti-intracranial infection therapy based on the binding of dehydroascorbic acid (DHA) and GLUT1 (Figure 12) [200,201].

3.2.6 Shuttle peptide mediated BBB crossing—

Recently, shuttle peptides have received increasing attentions due to their low cost with rich source, reduced immunogenicity, and high chemical versatility (*e.g.*, amenable to chemical modifications). Shuttle peptides allow the transportation of a wide range of cargoes across the BBB, such as small molecules, genetic material, proteins, and nanoparticles. A lot of BBB shuttle peptides have been developed for the delivery of nanoparticles to improve their distribution in CNS.

Many shuttle peptides were developed depending on some ion channels, such as KC2S, ^{L}CDX, ^{R}CDX, apamin, RDPs, and MiniAp-4, and their corresponding intracellular transportation and recycling in the CNS (Figure 13) [202–208]. The natural BBB shuttle peptides or proteins that can target the brain could be either endogenous, such as GSH, hormones, and apolipoproteins, or exogenous, including neurotoxins and some certain viruses (Figure 13) [209–211]. Most of the BBB shuttle peptides were obtained from phage display biopanning or neurotropic biomolecules. In brief, a particular receptor is overexpressed in cells or *in vivo*. The phages that bind the receptors or accumulate in the brain are recovered and amplified through bacterial infection, titration and sequencing. An ideal receptor for BBB targeting of shuttle peptides should have higher expression in the luminal side of vasculature cells in brain than in the other tissues. In addition, it should have the capacity to mediate the transcytosis process, broad substrate interaction, and high turnover. Some receptors (*e.g.*, transferrin (TfR1) 40 and low-density lipoproteins (LDLRs)) with abundant expression on the BBB, by which the transcytosis pathway is mediated, have been widely applied. A number of corresponding BBB shuttle peptides, such as B6 which recognizes transferrin receptor (TfR), peptide-22 which has special affinity for low-density lipoprotein receptor (LDLR), have been developed to transport cargos across the BBB [212,213].

In addition, several BBB shuttle peptides with non-corresponding targeting receptor were obtained through the display biopanning of *in vivo* phage. For example, the shuttle peptide of TGN (a 12-aa peptide that was displayed by bacteriophage Clone 12–2) conjugated poly (ethyleneglycol)-poly (lactic-co-glycolic acid) (PEG-PLGA) nanoparticles showed significantly higher uptake by bEnd.3 cells than that of unconjugated nanoparticles. In addition, enhanced brain accumulation was observed in mice with administration of Pep

TGN conjugated nanoparticles compared with unconjugated nanoparticles [214]. Furthermore, improved therapeutic effects in glioblastoma and AD models have been obtained with administration of the shuttle peptides modified nanoparticles [215,216]. In one example, phage-displayed TGN peptide and an AS1411 aptamer, which are specific targeting ligands of the BBB and cancer cells, were conjugated to nanoparticles to construct a glioma cascade delivery system (AsTNP). *In vitro* cellular uptake experiments showed that AsTNP could target not only BECs but also tumor cells. In addition, three-dimensional tumor spheroid experiments further confirmed that AsTNP could penetrate the endothelial monolayers and tumor cells reaching the core of the tumor spheroids, which was very important for the glioma therapy [215].

3.2.7 Cells mediated BBB crossing—A series of specific cells from the body, including monocytes, macrophages and neutrophils, have been used for the cargo delivery through cell-mediated transportation [217,218]. These cells could be obtained from the inflammatory stage of any CNS diseases, and their strong communication ability enables them to reach the inflammatory site in brain, where the BBB disruption was induced by inflammation. It was reported that these cells could help deliver liposomes and other nanoparticles across the BBB. The internalization of nanoparticles into the cells as well as the loading efficiency of cell carriers were mostly based on the nanoparticles' surface coating [218]. It was reported that positively charged nanocarriers are easier to be uptaken by immunocytes and stem cells than neutral nanoparticles. The antiretroviral drugs (*e.g.*, indinavir (IDV), ritonavir (RTV), and efavirenz (EFV)) loaded positively charged nanoparticles prepared through high pressure homogenization had higher accumulation in mononuclear phagocytes (MP) than that of negatively charged nanocarriers. Recently, monocytes-mediated macrophages have been developed and shown excellent brain homing ability. The transportation of superparamagnetic iron oxide nanoparticle SHP30 was mediated by monocytes and good penetration in the inflamed brain region was obtained [218].

Despite the high potential, several issues prevent wide-spread use of the cell-mediated transportation, such as relatively low drug loading content in cell carriers, limited clearance efficiency of the therapeutic agents-loaded cells, and premature release of the carried agents [218]. In order to improve the cells mediated BBB crossing, cell membrane cloaked nanoparticles were developed as potential strategies for the delivery of drugs into the brain because they could transport across impermeable BBB and blood tumor barrier (BTB) to the site of disease [219,220].

3.2.8 Combinational strategies for BBB-crossing of nanomaterials—The above-mentioned strategies are often combined to enhance the BBB-crossing of nanomaterials, and thus improve the treatment outcome of CNS diseases. For example, angiopep-2 that can trigger the transcytosis and BBB crossing by recognizing the LRP-1 expressed on the BCECs, and CPP of TAT that can help increase the cell penetrating activity, were co-conjugated on the surface of nanoparticles for brain tumor delivery [221]. The results indicated that the dual-targeting nanoparticles (AnACNPs) had higher brain accumulation than the nanoparticles modified with single ligand. In addition, functional

magnetic nanoparticles with CPP-conjugation can improve the brain accumulation due to the CPP-mediated BBB crossing and temporary disruption of BBB induced by magnetic gradients.

The CPP of TAT could penetrate the intact BBB with very high effiency for delivering proteins and nanoparticles into brain [222,223]. Combination of CPP-mediated and shuttle peptide-mediated BBB crossing can be used to improve the cargoes' delivery efficiency into the CNS. Recent *in vitro* and *in vivo* studies showed that dual-peptides modified liposomes with either T7-TAT, Angiopep-2-oligoarginine, or Tf combined with TAT, have a higher BBB penetration or transportation effect than that with a single peptide [224,225]. Overall, the CPPs with BBB penetrating capability and the ligands that mediate BBB crossing can be combined into a single nanocarrier system to enhance the BBB-crossing efficiency of nanomaterials [226].

3.3 Nanomaterial-based BBB crossing mechanisms

According to the above-mentioned nanomaterial-based BBB crossing strategies, the nanomaterial-based BBB crossing mechanisms can be classified into two categories: 1) invasive mechanism; 2) non-invasive mechanism. For the invasive mechanism, the BBB needs to be opened *via* physical means, and the nanomaterials are transported across the BBB through paracellular pathway. The above-presented temporary BBB disruption strategy and local delivery strategy belong to the invasive mechanism, which is also called paracellular mechanism. For the non-invasive mechanism, the BBB is intact during the drug delivery process, and the nanomaterials are delivered across the BBB *via* transcellular pathway. All of the above-discussed intranasal delivery strategy, CPP mediated BBB crossing strategy, receptor mediated BBB crossing strategy, shuttle peptide mediated BBB crossing strategy, and cells mediated BBB crossing strategy belong to the non-invasive mechanism, which can be named as transcellular mechanism as well.

4. Clinical study

Several clinical trials for the theranostics of CNS diseases based on nanomaterials have been developed. For example, the ultrasonic trial (), which aims to safely open the BBB prior to chemotherapeutics administration in patients with recurrent glioblastoma, is ongoing and sufficient data for the transient BBB disruption with SonoCloud system has been achieved [227]. Many studies based on the convection-enhanced delivery were performed for the treatment of glioblastoma or imaging in a surgical MRI suite (*e.g.*,). Magnetic nanoparticles, which hold great BBB-crossing ability under the magnetic field, have been developed for the theranostic of CNS diseases in clinical trials (NC100150) [228].

In addition, clinical trials were also performed for several BBB shuttle peptides, such as Angiopep-2 and GSH. Besides, several other BBB shuttle peptides are at pre-clinical stages. Through using the paclitaxel (ANG1005 or GRN1005) conjugated Angiopep-2, which is a BBB shuttle peptide and can interact with LRP1 [229,230], good tolerance has been obtained, and a Phase II clinical trial for treating recurrent high-grade glioma in combination with bevacizumab is currently ongoing () [231,232]. Furthermore, Angiopep-2 has been used for the transportation of various drug-loaded nanomaterials into the CNS. For example,

excellent improvement of locomotor activity and recovery of dopaminergic neurons were obtained with hGDNF-loaded nanoparticles with conjugation of Angiopep-2 in a rat PD model [233].

The BBB shuttle peptide GSH was developed for drug delivery and reached clinical trial. GSH was used for targeted delivery of the drug-loaded PEGylated nanoliposomes. The application of the glutathione PEGylated liposomes (G-Technology®) based doxorubicin delivery formulation (2B3–101) for the treatment of brain tumor is under Phase I/IIa clinical trial (). This nanocarrier system was further developed for the delivery of methylprednisolone (2B3–201) reaching its transportation efficiency up to 6.5-fold over free methylprednisolone [234], which substantially reduced neuroinflammation in rat encephalomyelitis model, and progressed into Phase I trial to treat multiple sclerosis () [235].

5. Conclusions and future perspective

The BBB plays a very important role in maintaining normal physiological function of CNS. Although the mechanism of many brain pathologies is still not fully elucidated, the leading reason is thought to be the BBB disruption. With the rapid development of nanobiotechnology, nanomedicine has shown great potential in the theranostics of neurological disorders. Although many nanomaterials have been approved by FDA or advanced into clinical trials, the clinical use of nanomaterial-based brain drug delivery systems is still limited mainly due to the following possible factors: 1) the study methods of *in vitro* and *in vivo* models for the BBB-crossing still need to be further developed; 2) the safety and side effects of nanomaterials remain to be studied; 3) the influence of the properties of nanocarriers, including surface properties, particle size, loaded agents and host materials, on BBB-crossing still needs to be further evaluated. Therefore, more fundamental studies on the nanomaterial-based BBB crossing strategies and drug release in the brain still need to be carried out in more details. For example, up to now, no systematic works have been studied on elucidating how physical-chemical properties of nanomaterials affect their transportation and localization in CNS. In addition, research works on nanomaterials for BBB crossing and specific brain cell targeting, which may improve the therapeutic effect of neurodegenerative disorders, are also expected, *e.g.*, design of nanomaterials that target to the dopaminergic neurons for the PD therapy, microglia cells for neuroinflammation, and neural stem cells for neuronal repairing. Furthermore, the development of nanomaterials for the BBB-crossing should focus on solving the following problems: 1) increase drug loading content; 2) enhance brain-targeting effect *via* conjugation of ligands; 3) develope more types of effective therapeutic agents, and more kinds of effective and safe biomaterials. With the development of new biomaterials and nanotechnologies, more effective brain-targeting nanomaterials capable of BBB-crossing will be designed for brain drug delivery. Therefore, nanomaterial-mediated BBB-crossing will have a broader prospect and could be a promising direction for the treatment of CNS diseases in the future.

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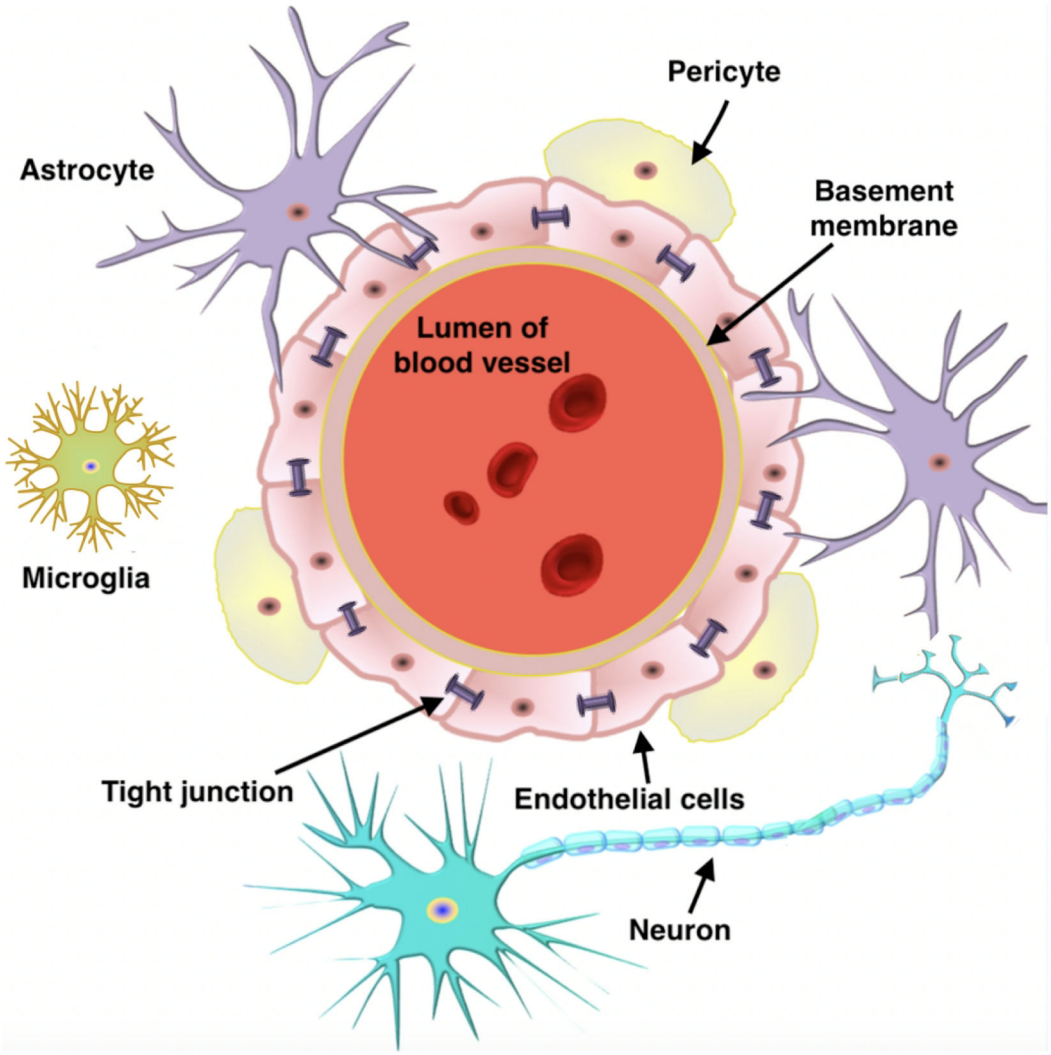

Figure 1.
Schematic illustration of the BBB.

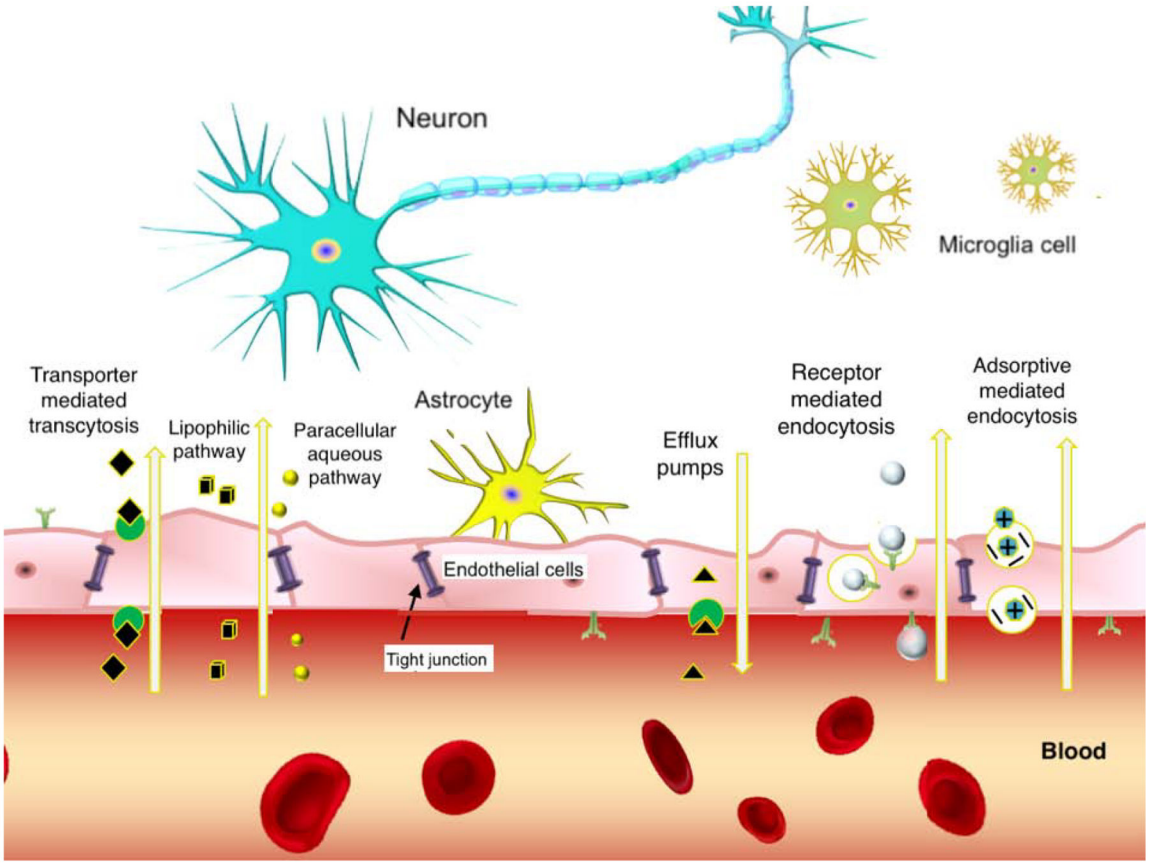

Figure 2.
Permeation mechanism of the BBB.

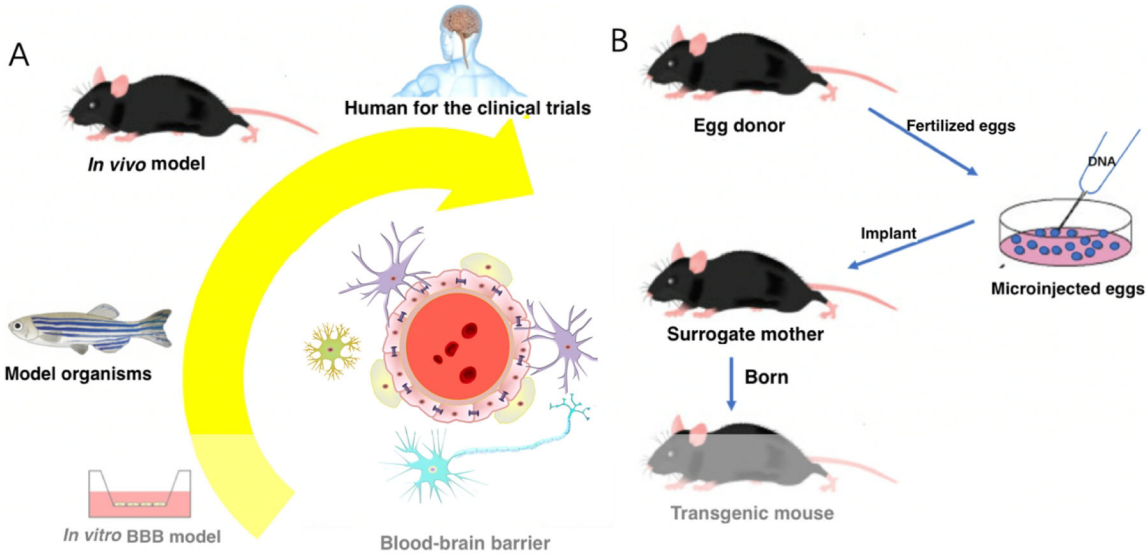

Figure 3.

(A) The models for studying the BBB crossing of nanocarriers. (B) Building process for *in vivo* BBB models.

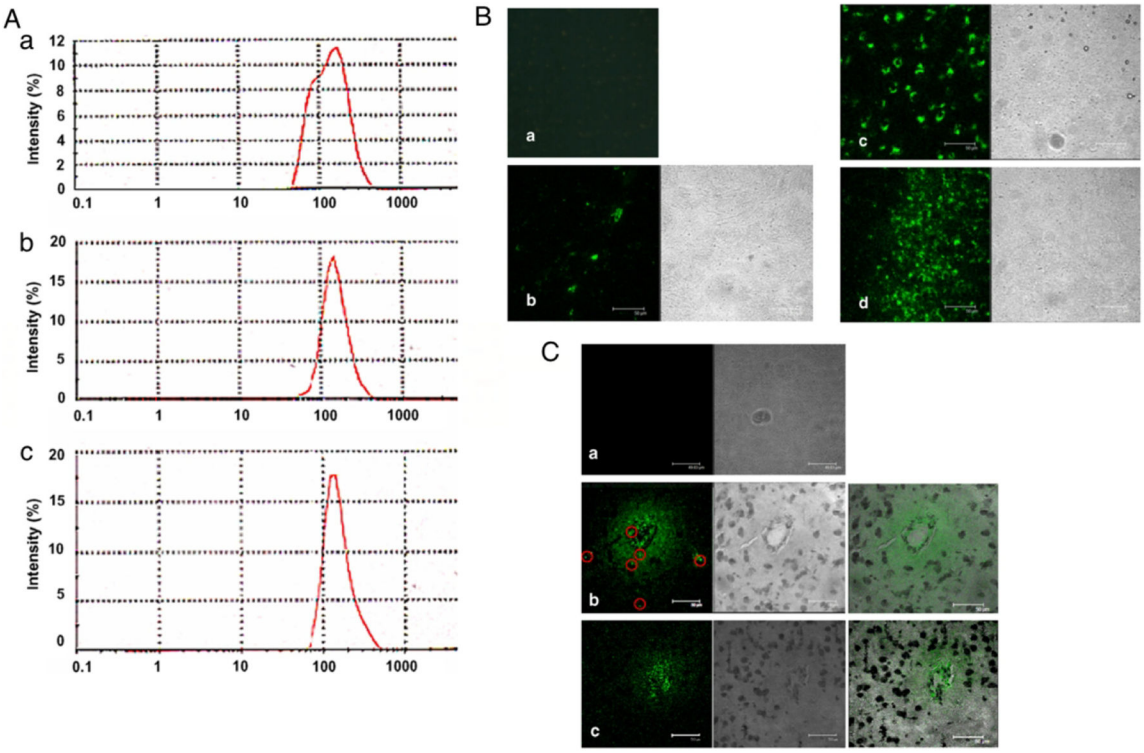

Figure 4.

Delivery of nanoparticles to the brain detected by fluorescence microscopy [110]. (A) Size distribution of PBCA nanoparticles determined by dynamic light scattering. (a) FITC-dextran-loaded nanoparticles, (b) rhodamine-123-loaded nanoparticles, (c) doxorubicin-loaded nanoparticles. (B) Cerebral distribution of administrated FITC-dextran-loaded nanoparticles through the carotic artery in the brain of rat. (a) Uncoated nanoparticles and administration of Tween 80-coated PBCA nanoparticles at (b) 20 min with fluorescence mainly shown in the lumina of brain capillaries, (c) 30 min with nanoparticles fluorescence mainly shown in brain capillary endothelial cells, and (d) 60 min with fluorescence spread distributed in brain, which indicates the BBB-crossing of nanoparticles. (C) Cerebral distribution of administrated rhodamine-123 labelled nanoparticles through a tail vein in the brain of rat. (a) no fluorescence signal in brain could be observed at 60 and 120 min after administration of uncoated PBCA nanoparticles (one time point was shown). (b) Fluorescence signal can be observed in the brain capillary lumen, the endothelial cells and the perivascular brain tissue at 60 min after administration of polysorbate 80-coated nanoparticles. Including, the red circles indicated the identified nanoparticles. (c) The fluorescence signal could be observed throughout the brain tissue after nanoparticles has been administrated for 2 hours. Copyright 2008, Elsevier.

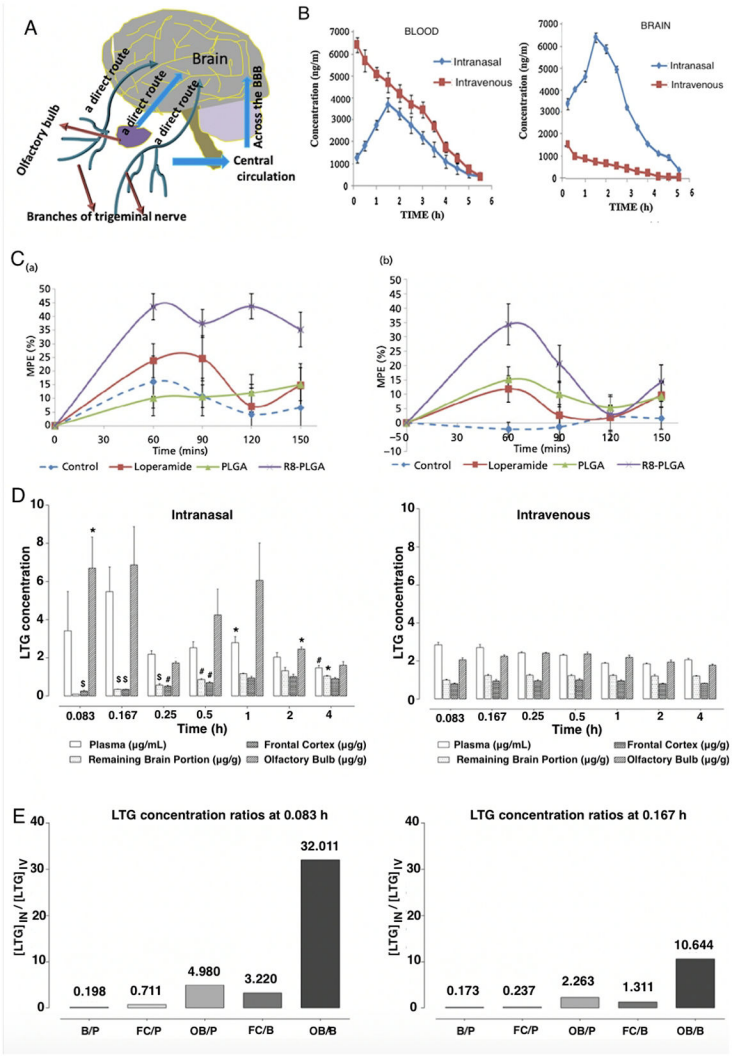

Figure 5.

Drug delivery to the brain with intranasal administration (A) Schematic of the drug delivery to the brain from the nasal cavity. (B) concentration-time profile of OND loaded NLC in (a) Blood and (b) Brain with intranasal and intravenous administration (n = 3). Higher concentration of OND loaded NLC in brain with intranasal administration than that of intravenous administration [113]. Copyright 2014, Elsevier. (C) Maximum possible effect (MPE %) of antinociceptive effect by loperamide in mouse with administration of PLGA and R8-PLGA nanoparticles (a) intranasally and (b) intravenously. R8-PLGA versus control, i.n. $P < 0.05$ and i.v. $P < 0.05$ at $t = 60$ min [112]. Copyright 2015, Wiley-blackwell. (D) Lamotrigine (LTG) concentrations up to 4 h post-dosing in plasma and different brain regions of mice after intranasal (IN) and intravenous (IV) administration (4 mg/kg, n = 4). Statistical significant differences between IN and IV administrations are marked with (*) for $p < 0.05$, (#) for $p < 0.01$ and (§) for $p < 0.001$. After IN administration, higher LTG concentrations in the olfactory bulb relatively to other areas of the brain was found, which indicates a potential direct nose-to-brain transport pathway for IN administration of LTG [117]. (E) Relationship between tissue-to-plasma and tissue-to-remaining portion in the

brain of mice with LTG concentration ratios obtained at 0.083 h and 0.167 h after IN and IV administration (4 mg/kg). Including, B/P is remaining portion of the brain / plasma ratio; FC/B is frontal cortex / remaining portion of the brain; FC/P is frontal cortex / plasma ratio; OB/B is olfactory bulb / remaining portion of the brain ratio; OB/P is olfactory bulb / plasma ratio. The result indicates that a direct transport from nose to brain for LTG may be involved [117]. Copyright 2015, Elsevier.

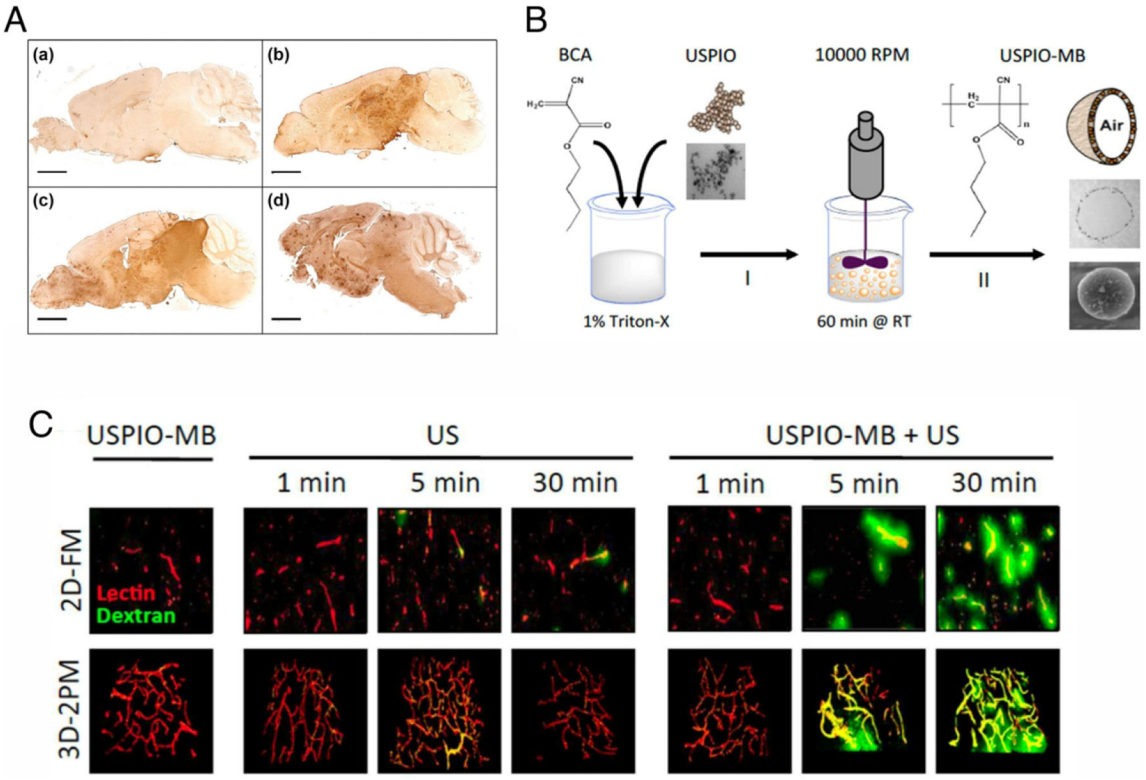

Figure 6.

BBB disruption: (A) The transgene expression of TPP1 affected by the increasing mannitol induced BBB disruption was shown in immunoperoxidase staining images. Each mouse was administrated with 3.18×10^{10} gc of AAVrh.10CLN2 after (a) 125 μl, (b) 250 μl, (c) 500 μl, or (d) 750 μl of mannitol, respectively. At 125 μl, no transgene expression is seen. At 250 μl, some transgene expression production can be seen in deeper brain structures and increasing staining production could be observed in cortical structures with the mannitol dose reaching to 500 μl and 750 μl [121]. Copyright 2014, Elsevier. (B) Schematic synthetic protocol of ultrasmall superparamagnetic iron oxide-loaded microbubbers (USPIO-MB) [133]. (C) Extravasation and penetration of FITC-dextran (green). FITC-dextran extravasation crossing the rhodamine lectin-stained vessels (red) as shown in 2D fluorescence (2D-FM) and 3D two-photon microscopy (3D-2PM) images, which indicating efficient transport of macromolecular drug crossing the BBB with the combination of USPIO-MB within 5 and 30 min of US [133]. Copyright 2015, Wiley-blackwell.

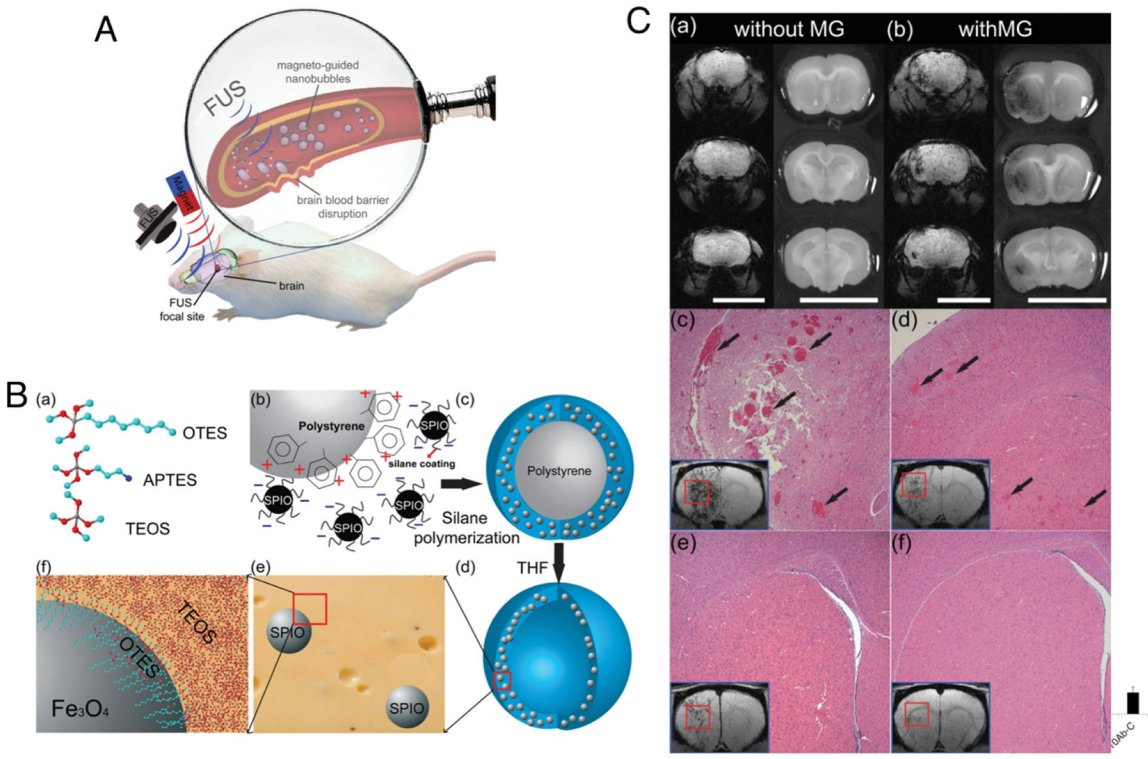

Figure 7.

A multitheragnostic nanobubble system to induce BBB disruption with magnetically guided (MG) focused ultrasound. (A) Schematic diagram of the experimental setup to demonstrate the concept of disrupting the BBB with the locally accumulated magnetically guidable theranostic nanobubbles (MNBs) in a specific brain area after applying magnetic guidance in vivo and the local accumulation of MNBs in the vasculature to perform dual targeting of the BBB disruption. (B) The schematic of the synthesis of MNBs and the interfacial structure of the SPIO/silica. (a) The fabrication procedure involved a mixture of silane monomers of TEOS, OTES, and APTES. (b) Monodispersed positively charged PS particles were mixed with negatively charged SPIO, and then (c) a silica shell was grown onto the PS core particles and mixed with SPIO nanoparticles. (d) Hollow MNBs formed after treatment with THF overnight. (e) The silica shell presented as a nanoporous structure with embedded SPIO nanoparticles. (f) The OTES was very compatible with the oleic acid-conjugated SPIO and the OTES polymerized with TEOS to form the shell on the PS core. (C) (a) and (b) represents the efficiency of MG on 500 nm MNB-mediated FUS-BBB disruption as evaluated by the representative images of *T*2* gradient echo coronal sections and their corresponding EB dye-stained images, the scale bar is 1 cm. Representative images of *T*2*-MRI sections and their corresponding H&E stained slices were used to investigate the BBB permeability and hemorrhagic damage from c) MG-assisted FUS-exposure with 2000 nm MNBs, d) 1000 nm MNBs. e) 500 nm MNBs, and f) 200 nm MNBs, respectively. Including, tissue destruction and hemorrhage were found in the mouse striatum where SPIO-embedded 2000 nm, 1000 nm, and 500 nm MNBs [132]. Copyright 2015, Wiley-blackwell.

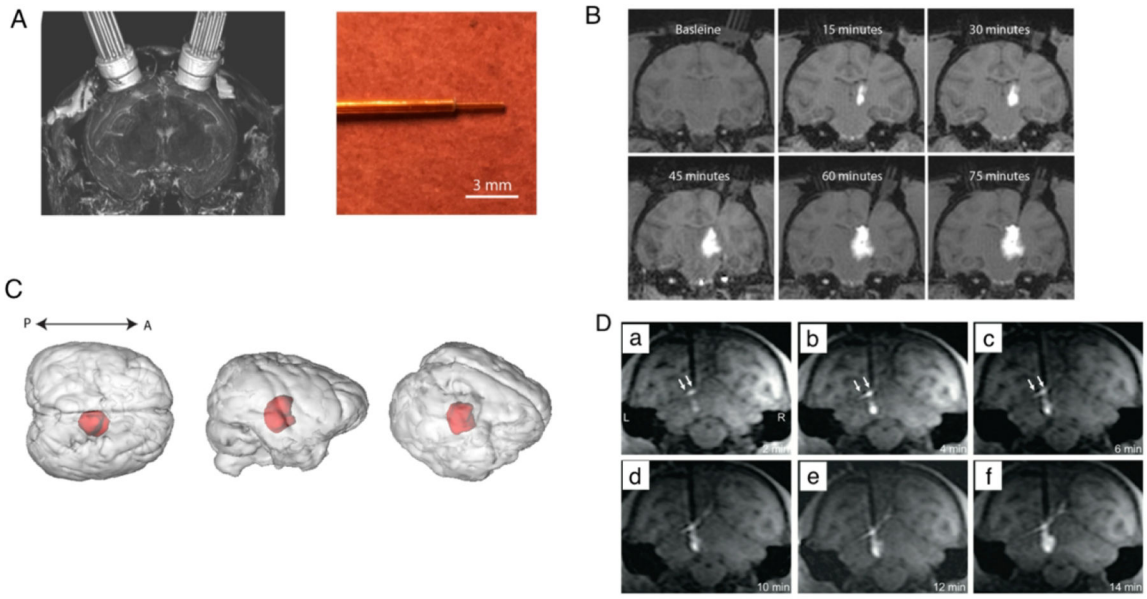

Figure 8.

Transportation of nanoparticles into CNS with CED infusions. (A) the implanted cannula guide cylinders were shown in 3D MR image (left and the tip of the reflux-resistant injection cannula was shown in photography (right). (B) the growing distribution volume of the viral vector during the medial thalamic infusion in NHP-H as shown in a set of real-time MR images of coronal sections. (C) Showing the reconstruction (red) of the MR volume of the spread of viral vector with CED infusion [142]. Copyright 2018, Elsevier. (D)Real-time (14 min) MRI convection-enhanced delivery in the NHP cerebellum with infusion of AAV5-GFP/Gd, shown as hyper-intense regions indicative of MRI contrast, denote placement of cannula tip within the cerebellar cortex. Obvious increase in infusate size was obtained accompanying with the extending of infusion time and increasing of delivered volume [144]. Copyright 2018, Mary Ann Liebert.

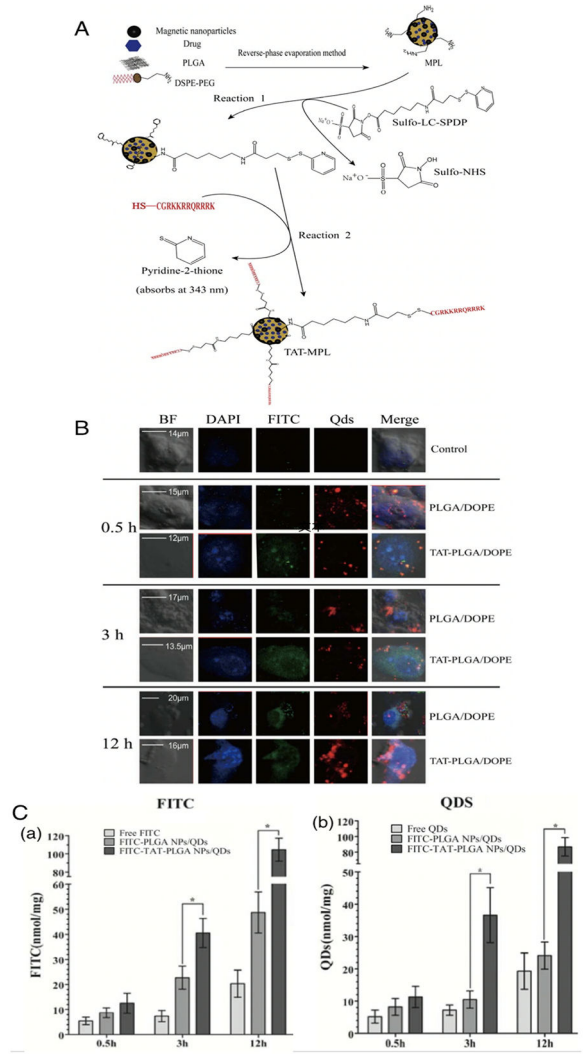

Figure 9.

CPP-mediated transportation of nanoparticles across BBB. (A) preparation schematic of stealth magnetic PLGA/Lipid nanoparticles (MPLs) with conjugation of TAT peptide onto MPLs. (B) Localization of QDs encapsulated TAT peptide modified MPLs in brain endothelial cells. Cells were cultured in FITC-labeled QDs-loaded NPs-containing medium for 0.5, 3, and 12 h, respectively, and DAPI treating was performed for these cells before observation with a confocal microscopy. High fluorescence signal was observed in the cytoplasm and cell nucleus for the sample administrated with TAT-MPLs, which indicates effective delivery of QDs to bEnd.3 cells for these nanoparticles. (C) Quantitation of QD-loaded FITC-MPLs and QD-loaded FITC-TAT-MPLs in brain endothelial cells. Cells were cultured in a 24-well plate for lysed, and the fluorescence intensity of FITC (a) and QDs (b) in cells were measured with a microplate spectrophotometer at 0.5 h, 3 h, and 12 h, respectively. conjugation of TAT peptide on MPLs could significantly improve the cellular uptake of cargoes in bEnd.3 cells through penetrating the cell membrane. This is a promising strategy in designing nanocarriers for crossing the BBB and transporting drugs into the CNS [158]. Copyright 2014, Public Library of Science.

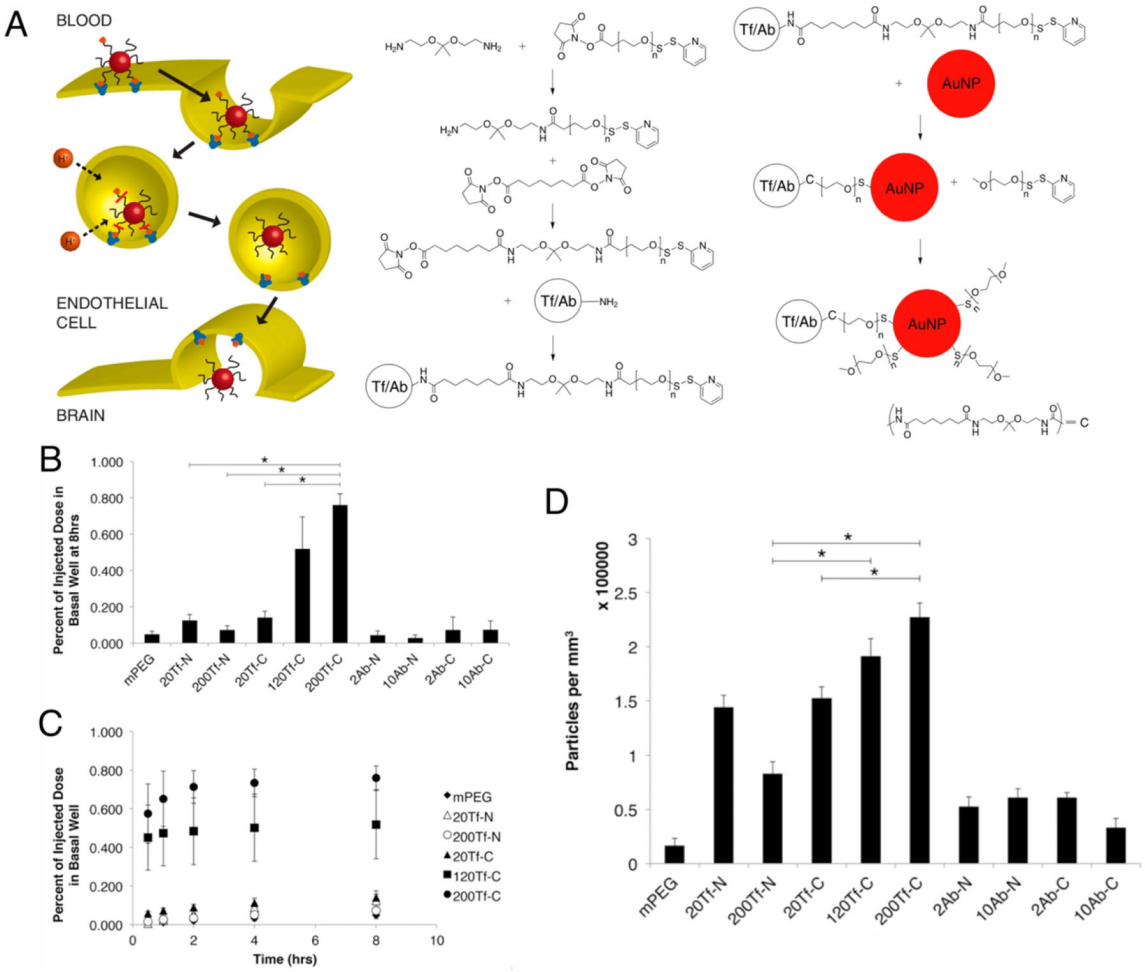

Figure 10.

Receptor-mediated nanoparticles crossing the BBB. (A) The transportation mechanism of Tf-containing gold nanoparticles with an acid-cleavable linkage across the BBB and preparation of acid-cleavable Tf/Ab-DAK-PEG-OPSS ligand and the targeted gold nanoparticles. Disruption of the linkage between Tf and the nanoparticle core after being uptake by brain endothelial cells through endocytosis pathway due to the acidification in the endosome, which enable the free transport of the nanoparticle into the CNS across BBB. (B) The percentage of various nanoparticles reaching the basal well of bEnd.3 coated transwells 8 h after administration. 120Tf-C and 200Tf-C show greater ability to cross the transwells compared with 200Tf-N, whereas both Ab-C nanoparticles did not show a significant increase compared with equivalent Ab-N formulations. (C) The percentage of Tf-containing nanoparticles crossed the BBB model over time. Note that most crossing behavior happened within the first 2 h for all Tf-C nanoparticles. *$P < 0.001$. (D) The gold nanoparticles accumulated in the brain parenchyma were evaluated with silver enhancement of brain sections. The result indicates that addition of acid-cleavable linkage DAK could improve the transport effective of high-avidity Tf-containing nanoparticles entering into the brain [167]. Copyright 2015, National Academy of Sciences.

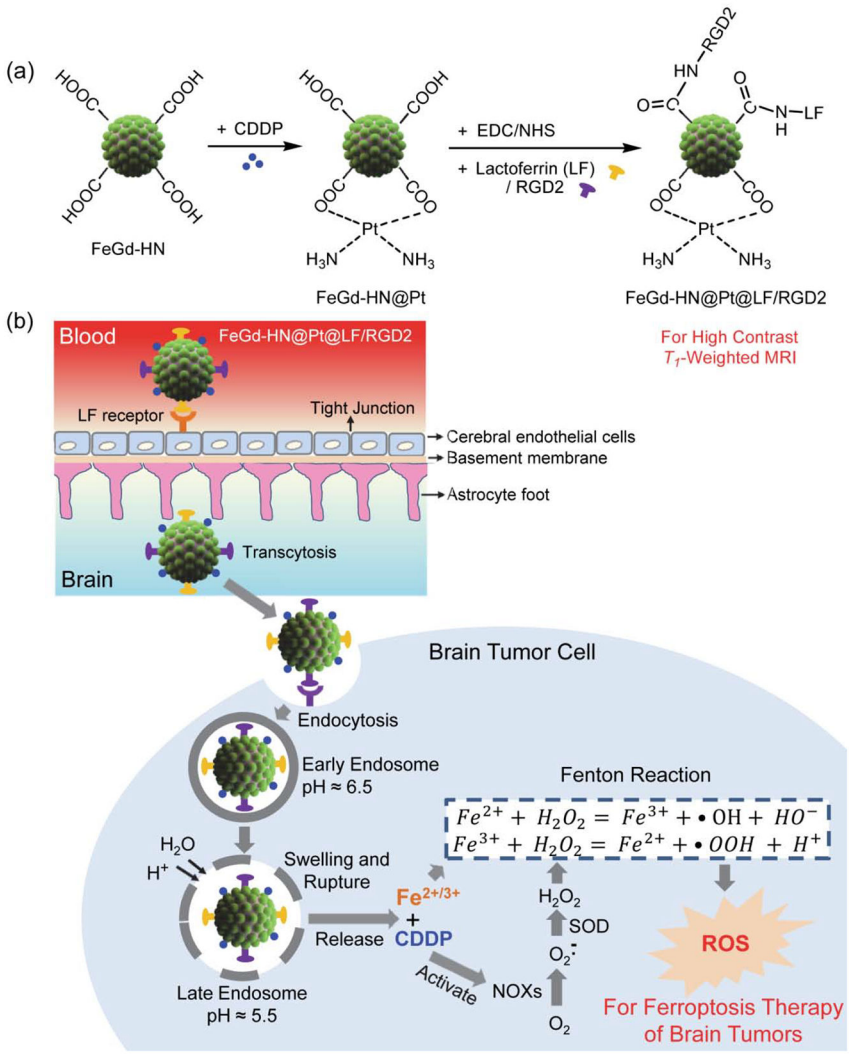

Figure 11.

(a): Design and synthesis of the Fenton-reaction-acceleratable magnetic nanoparticles, i.e., cisplatin-loaded Fe_3O_4/Gd_2O_3 hybrid nanoparticles with conjugation of LF and RGD2 (FeGd-HN@Pt@LF/RGD2). (b): Mechanism illustration for the ferroptosis therapy (FT) of orthotopic brain tumors with self-MRI-monitoring [175]. Copyright 2018, American Chemical Society.

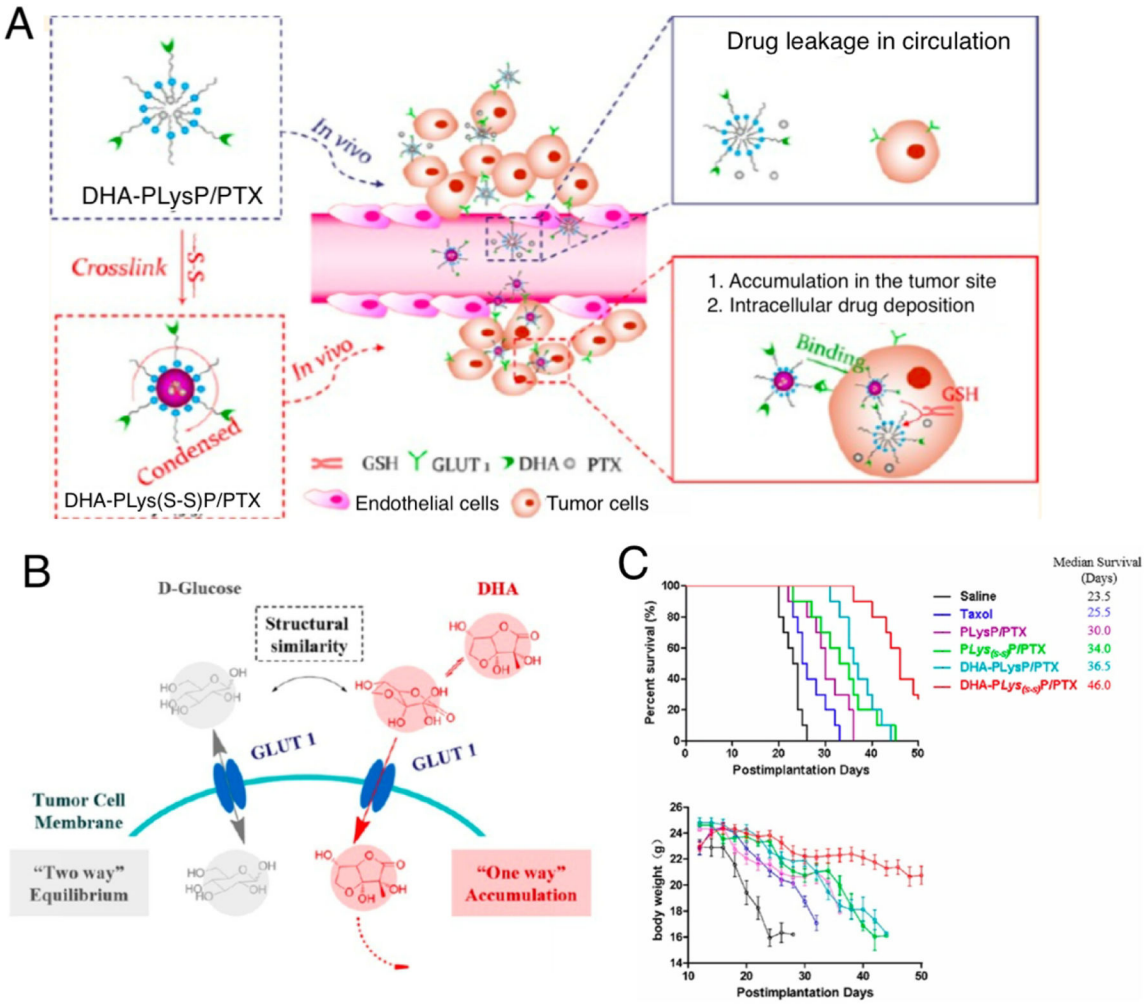

Figure 12.

Glucose transporter isoform 1 (GLUT1) mediated BBB-crossing for nanodevices. (A)The mechanism of the smart therapeutic nanocarrier with cooperative dual characteristics of high tumor-targeting ability and selectively controlling drug deposition in tumor cells was developed. The disulfide linkage contributes a reductive-sensitive characteristic for the nanodevice, which shield the loaded drug from leaking in blood. Dehydroascorbic acid (DHA) was modified on the surface of nanodevice for tumor-specific targeting via binding to GLUT1, a glucose transporter abundant expressed on tumor cells. (B) Different transportation characteristics of D-glucose and DHA by GLUT 1. A "two-way" transportation of D-glucose to keep its stable concentration in cells. DHA rapidly reduced to ascorbate, which effectively is "trapped" within the cell. (C) The Kaplan-Meier survival curves and body weight of glioma-bearing mice treated with different PTX formulations at days 12, 15, and 18 postimplantation (n = 15), which indicates that this nanodevice could be a promising potential platform for the treatment of glioma [200]. Copyright 2014, American Chemical Society.

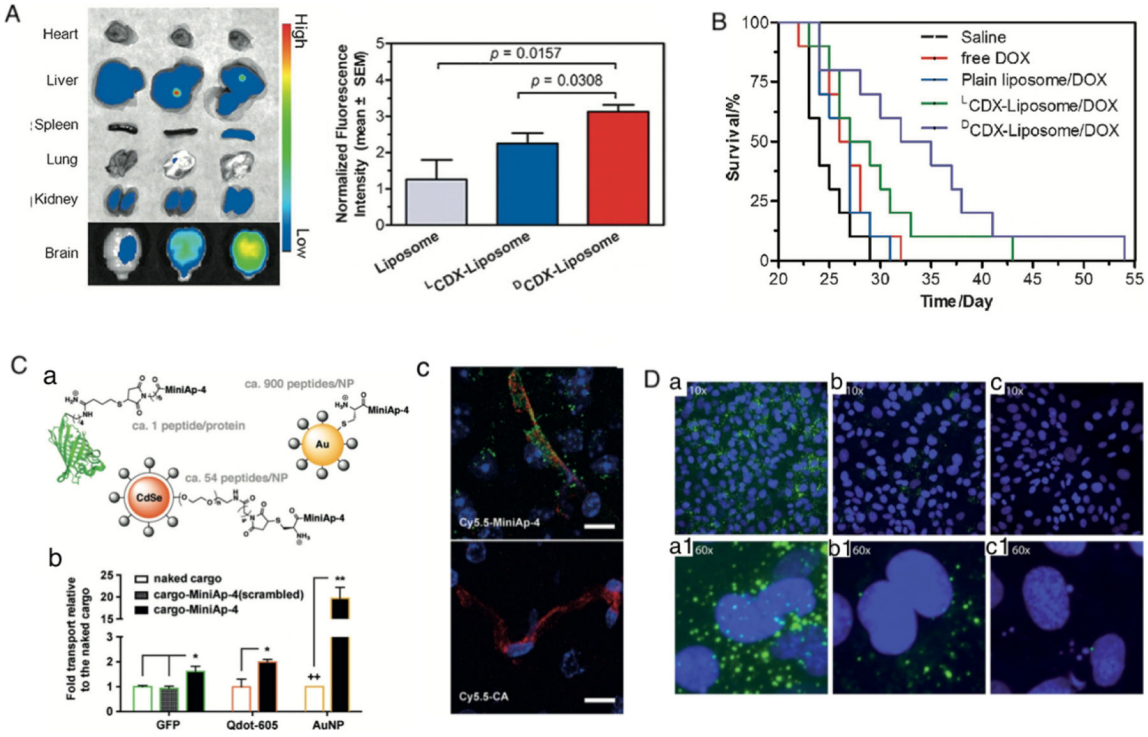

Figure 13.

The BBB shuttle peptides mediated BBB-crossing. (A) Ex vivo imaging of dissected tissues of different organs and the fluorescence intensity of brain in the mice 8 h after injection of plain liposomes, ^{L}CDX-liposomes, and ^{D}CDX-liposomes, respectively. (B) Kaplan-Meier survival curves of intracranial U87 glioblastoma beared mice, which shows that the mice administrated with DOX-loaded ^{D}CDX or ^{L}CDX-liposomes survived much longer than the control groups that administrated with saline, free DOX, and DOX-loaded plain liposome. These results showed that ^{D}CDX transport could be developed as a good shuttle for brain targeted drug delivery [207]. Copyright 2015, Wiley-VCH. (C) MiniAp-4 was designed as a BBB shuttle. a) MiniAp-4 was conjugated onto the protein and nanoparticles as a shuttle. b) the permeability of MiniAp-4 modified protein and nanoparticles was improved comparing with that of non-MiniAp-4 modification in the human-cell-based *in vitro* BBB model (n = 3, *p < 0.05, **p < 0.01, ***p < 0.001). + + indicates the quantification limit. c) higher fluorescence signal (green) was shown in the representative confocal microscopy images of brain slices in mice administrated with Cy5.5–MiniAp-4 (top) than that of Cy5.5–CA (bottom). Scale bars represent 10 mm [204]. Copyright 2016, Wiley-VCH. (D). CF signal in RBE4 cells with incubation of (a): GSH-PEG liposomes at 37°C, (b): PEG liposomes at 37 °C, (c): GSH-PEG liposomes at 4 °C, respectively. More uptake of the GSH-PEG liposomes in cells comparing with that of PEG liposomes at 37 °C was obtained as conformed from the fluorescent signal due to the targeting effect of GSH. Moreover, the decreased uptake at 4 °C demonstrates an active uptake mechanism for the GSH-included liposome [209]. Copyright 2014, Taylor & Francis.