



Recent advances in the development of nanomedicines for the treatment of ischemic stroke

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ABSTRACT

Ischemic stroke is still a serious threat to human life and health, but there are few therapeutic options available to treat stroke because of limited blood-brain penetration. The development of nanotechnology may overcome some of the problems related to traditional drug development. In this review, we focus on the potential applications of nanotechnology in stroke. First, we will discuss the main molecular pathological mechanisms of ischemic stroke to develop a targeted strategy. Second, considering the important role of the blood-brain barrier in stroke treatment, we also delve mechanisms by which the blood-brain barrier protects the brain, and the reasons why the therapeutics must pass through the blood-brain barrier to achieve efficacy. Lastly, we provide a comprehensive review related to the application of nanomaterials to treat stroke, including liposomes, polymers, metal nanoparticles, carbon nanotubes, graphene, black phosphorus, hydrogels and dendrimers. To conclude, we will summarize the challenges and future prospects of nanomedicine-based stroke treatments.

1. Introduction

Stroke has received widespread attention because of its serious threat to human health and well-being [1]. It is expected that by 2030, the number of stroke cases and related deaths will rise to 23 million and 7.8 million, respectively. Stroke is caused by an abrupt reduction of blood flow to the brain because of an embolus, a blood clot. Cerebral ischemia triggers a complex cascade of biochemical reactions due to reduced glucose and oxygen delivery, resulting in a substantial decrease in mitochondrial adenosine triphosphate (ATP) levels. The stroke cascade immediate glutamate excitotoxicity, oxidative stress and inflammation that contribute to tissue injury [2–4]. Because of the complexity of pathophysiological responses following a stroke, few therapeutic approaches have clinical efficacy [5]. The only approved

treatment for embolic stroke is recanalization induced by the application of recombinant tissue plasminogen activator (rt-PA) [6,7]. However, this approach is limited by a narrow therapeutic window (<4.5 h) and complications in some patients.

According to the recent literature, only 3 positive phase III randomized clinical trials (RCTs) have been conducted for acute ischemic stroke. They validate the clinical effect of intravenous (IV) tPA for acute ischemic stroke within 3 h; Prolyse in Acute Cerebral Thromboembolism (PROACT) II demonstrated efficacy of IV tPA in selected patients out to 4.5 h; European Cooperative Acute Stroke Study (ECASS III) demonstrated the clinical and recanalization effect of intra-arterial (IA) prourokinase in the treatment of M1 or M2 middle cerebral artery occlusion within 6 h of a stroke.

Recently, nanomedicine delivery systems have gained some

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attention as effective and safe systems for the delivery of therapeutic agents across the BBB [8]. Limited success is due to their ability to penetrate the blood brain barrier via both passive and active targeting mechanisms, resulting in enhanced accumulation in brain (see Fig. 1).

2. Pathophysiology of ischemic stroke

2.1. Excitotoxicity

One of the molecular mechanisms responsible for ischemic damage is excitotoxicity [9]. Energy failure induces rapid release of excitatory amino acids, as well as inhibited reuptake of the excitatory amino acids. The high concentration of glutamate in synapses activates metabotropic glutamate receptors such as AMPA and NMDA receptors [10,11], resulting in disruption of calcium homeostasis. The initial calcium influx following excitotoxic glutamate stimulation is known to cause a secondary intracellular calcium overload, and this secondary response leads to a deleterious cascade of metabolic events through oxidative stress-mediated mechanisms such as apoptosis and inflammation (Fig. 2).

2.2. Oxidative and nitrosative stress

High oxygen consumption, high oxidized lipids levels as well as low endogenous antioxidant capacity in brain can cause the antioxidant defense system to be insufficient to scavenge free radicals (reactive oxygen and nitrogen species), resulting in oxidative and nitrosative stress-induced injury [13]. Free radical formation has been shown to be increased following a stroke and is thought to play a role in stroke damage. Reactive oxygen (ROS) and nitrogen species (RNS) may be important mediators of tissue injury in ischemic stroke [14]. ROS have many adverse effects at the cellular level, including the destruction of cellular macromolecules, induction of apoptotic cell death via lipid peroxidation; they cause oxidative DNA damage, protein annihilation, chemotaxis, and cytoskeletal structural injury [15]. Additionally, ROS and subsequent oxidative stress affect the cerebral vasculature by disrupting the functional integrity of BBB due to changes in the molecular organization and expression of critical tight junction proteins, such as claudin-5 and occludin at the BBB [16].

The NO molecule, produced by NOS, which is activated by ischemia, can combine with superoxide to produce peroxynitrite, which is an effective oxidant [17]. RNS also have prominent cellular effects, such as inhibition of mitochondrial enzymes, improving the opening of the mitochondrial permeability transition pore, and causing DNA damage. They also accelerate the influx of Ca^{2+} ions by activation of the cation channel subfamily M member 7 channels, which are permeable to the Ca^{2+} ions. Additionally, NO can affect cells due to its regulatory effect on important proteins, including metalloproteases, caspases, and glycolytic enzymes [18].

2.3. Inflammatory

After cerebral ischemia, the inflammatory cascade is activated and mediated by a wide variety of molecules such as cytokines and lymphokines released from injured tissues and ROS species. Ischemia also induces microglial (resident macrophages of the brain) transformation into phagocytic cells that generate various cytotoxic and/or cytoprotective substances. Microglia cells exert neuroprotective effects by releasing neurotrophic factors, including brain derived neurotrophic factor and insulin-like growth factor I. Also, in response to ischemia, activated microglia generate proinflammatory cytokines, such as interleukin- 1β (IL- 1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF- α) [19]. While the initial purpose of activated microglial is to protect neuron cells, the over-activation of microglia leads to deleterious inflammation and neuronal death [20].

In the brain, toll-like receptors (TLRs) are expressed on microglia, astrocytes, endothelial cells, and neurons [21]. Under hypoxic conditions, TLR4 is upregulated on the surface of microglial [22]. TLRs can activate transcriptional mediators that induce nuclear gene expression of pro-inflammatory factors, cytokines, and adhesion molecules. Moreover, endogenous ligands, such as Hsp70 are upregulated after ischemia, and could potentially cause ischemic damage via TLR activation.

3. Treatment strategies

For stroke treatment, time is a key factor. The first stroke therapeutic strategy aims to increase brain reperfusion by removing clots by pharmacological or mechanical means. tPA-induced thrombolysis and intravascular recanalization techniques are now both standard treatments for acute ischemic stroke, but both have a narrow time frame when they can be applied, and there is the risk of cerebral hemorrhage.

3.1. Tissue-type plasminogen activator

Recombinant rt-PA for thrombolysis is the only commercially-available pharmaceutical agent approved by the US FDA. After rt-PA treatment, brain re-oxygenation occurs quickly. However, this treatment has a narrow therapeutic window in order to be effective (no more than 4.5 h after symptom onset). Because of this, it is estimated that only 7% of patients can benefit from rt-PA administration [23]. In addition, in patients with large infarcts, rt-PA has a relatively low success rate, and can also increase the risk of bleeding [24].

In 2015, several randomized controlled trials showed that intravascular thrombectomy was superior to intravenous rt-PA to improve the prognosis of stroke in patients with proximal occlusion of the large arteries, and three of four patients had complete reperfusion. In addition, a comprehensive meta-analysis of eight RCTs revealed that mechanical thrombectomy was correlated with an increased probability of positive outcome when compared with standard rt-PA treatment [25]. Moreover, mechanical thrombectomy, after treatment with rt-PA is now regarded as a standard guideline-recommended therapy for patients with large vessel occlusion.

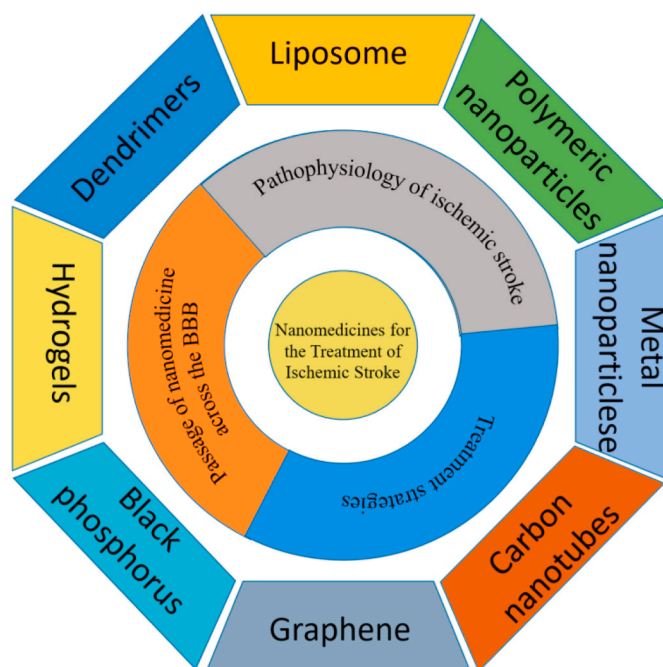


Fig. 1. Nano-medicine for the treatment of ischemic stroke.

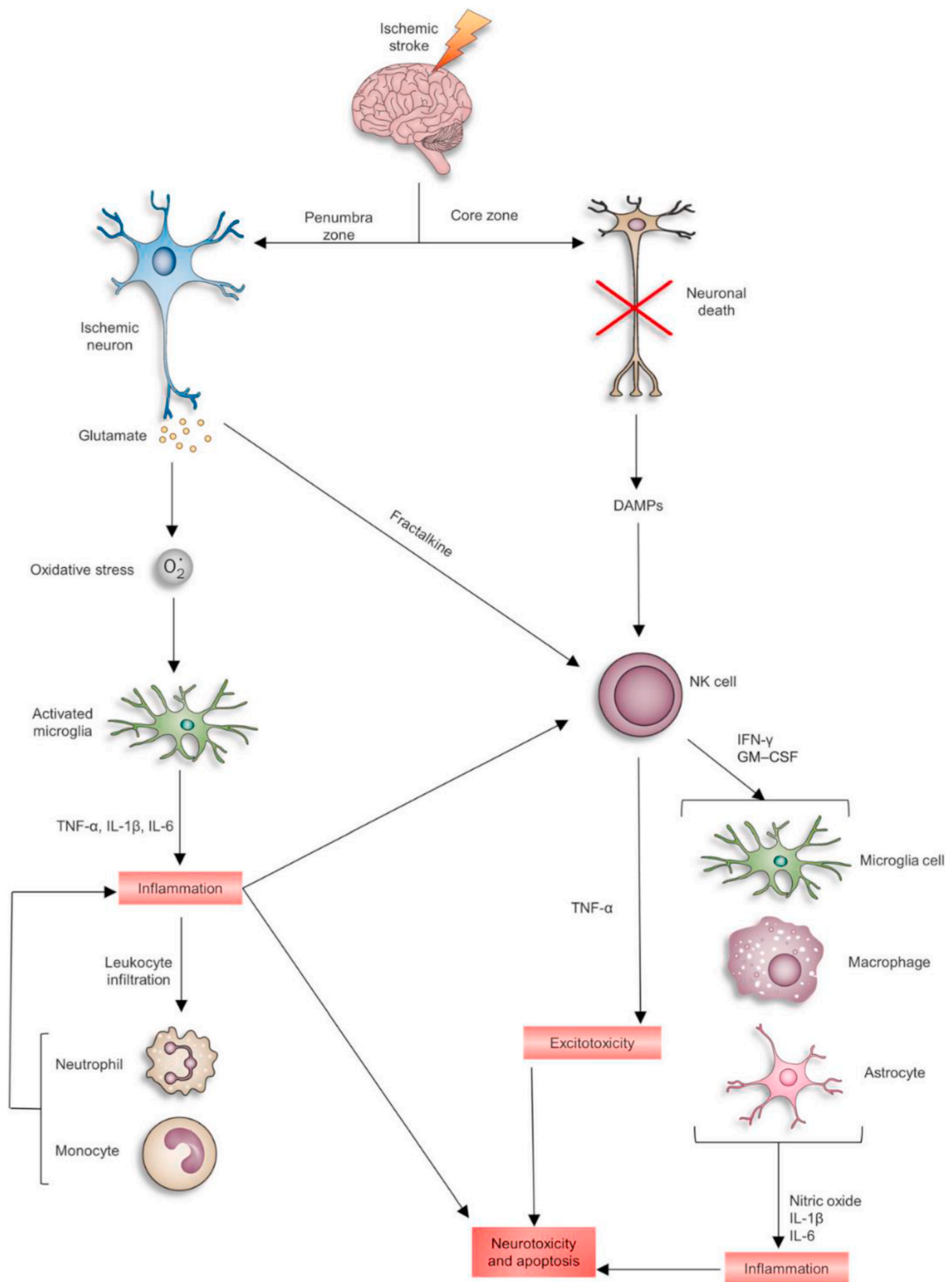


Fig. 2. Schematic of neurotoxicity induced by changes in inflammatory cytokines and immune cells after cerebral ischemia. Reprinted with permission from Ref. [12]. Copyright 2017 SPRINGER.

3.2. Neuroprotective agents

As mentioned above, during ischemic cell death, several mechanisms play an important role, including excitotoxicity, oxidative and

nitrosative stress, and inflammation. Neuroprotection is thought to be a potential method to modulate one or more of these mechanisms. These interventions include drug-induced neurotransmitter receptor blockade, anti-oxidants, anti-inflammatory drugs, and inhibition of cell death

pathways [26].

In the past two decades, more than 1000 neuroprotective agents have been developed and studied to some extent, and more than 100 have progressed to clinical trials, most of which were poorly conceived and designed. It is not surprising that none of these drugs showed efficacy in randomized controlled trials.

Neuroprotection in the laboratory is mainly designed in the rodent model of transient cerebral ischemia [27], while the majority of patients in neuroprotection trials had permanent ischemia. About one-third (37%) of patients included in neuroprotection trials could receive thrombolytic treatment. The failure of most clinical trials could be attribute to lack of methodological rigor in preclinical studies, and the low BBB permeability of neuroprotectants is considered an obstacle.

3.3. Photothermal therapy

Photothermal therapy (PTT) has been widely used in the treatment of cancer [28–32]. In PTT, photothermal agents generate a localized increase in temperature to, achieve tumor ablation. Graphene and black phosphorus have also been employed in phototherapy of neurodegenerative diseases, offering advantages, including high therapeutic efficiency and minimal invasiveness [33–37]. In addition, improved BBB permeability of black phosphorus nanosheets could be achieved under NIR irradiation [38]. black phosphorus may also have additional therapeutic benefits, such as decreasing ROS and increased mitochondrial membrane potential (MMP).

In addition to the direct cytotoxic effect of photothermal therapy, lasers may also be used to promote smart drug release [39–42]. Qiu et al. [43] designed a fully biodegradable black phosphorus hydrogel as a smart drug release platform. After loading the drug by electrostatic adsorption, black phosphorus nanosheets were mixed with a low-melting-point agarose aqueous solution to obtain the black phosphorus hydrogel. The hydrogel is capable of reversible hydrolysis and softening with an increase in temperature induced by the laser, thereby achieving photo-controlled release of the drug. The drug release rate of black phosphorus hydrogel is significantly improved under the irradiation compared with the dark condition. Light-controlled drug release may have clinical application for the treatment of stroke.

4. Passage of nanomedicine across the BBB

The BBB is an important barrier between the nervous system and other parts of the body. The BBB protects the brain from harmful stimuli. BBB permeability is controlled by tight junction protein complexes that limiting paracellular diffusion between capillary endothelial cells. Tight junction proteins complexes include occludin, claudins, junctional adhesion molecules, membrane-associated guanylate kinase-like proteins, and membrane associated degrading enzymes. There are specific mechanisms involved in the BBB transport of molecules that may be utilized for therapeutic drug delivery (Fig. 3).

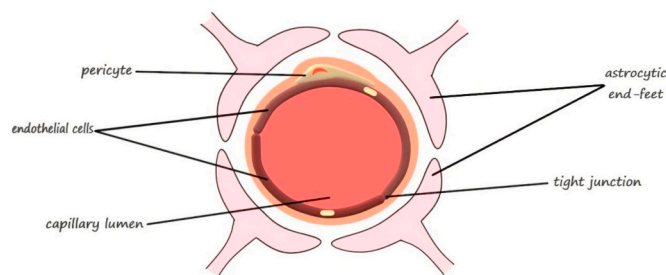


Fig. 3. Schematic illustration of the main structural components of the BBB. Reprinted with permission from Ref. [44]. Copyright 2018 MDPI.

4.1. Altered permeability of the BBB

After brain ischemia, oxidative stress induced by ROS production changes the grouping of tight junction proteins at the BBB, leading to heightened paracellular leakage [45]. Astrocytes also have a marked impact on the BBB destruction after ischemic injury by mechanisms that cause physical disruption of astrocyte–endothelial junctions, opening of paracellular channels, and digestion of BBB matrix proteins [46].

Ischemic stroke initiates the opening of BBB for a short period of time, about minutes to hours. The second long-term (hours to days) reopening is initiated by reperfusion of the ischemic zone, by restoring blood supply. BBB dysfunction (primary and secondary opening) allows for a variety of normally restricted substances, including proteins and red blood cells, to enter the damaged brain parenchyma. The leaky BBB provides opportunities for nanomedicines because of their small size and good fluidity.

4.2. Active BBB transport mechanisms

Another attractive strategy to promote transport of nanomedicines across the BBB is transcytosis. Active transport, including adsorptive-mediated and receptor-mediated transcytosis have been studies in order to achieve intercellular spacing and improve selective targeting. Positively charged nanoparticles interact with the negatively charged BBB luminal surface, leading to adsorption to endothelial membranes where they may be transcytosed. Coating nanomedicines with cationic biomolecules, for example, cell-penetrating peptides and cationic protein, is another promising way to increase BBB transport. Cell-penetrating peptides such as TAT improve BBB transit both in vitro and in vivo [47,48].

An alternative strategy for nanomedicine delivery across the BBB during the first few hours after injury is receptor-mediated transcytosis. Antibodies, ligand-mimicking peptides or whole ligands can be functionalized to nanoparticles targeting receptors on the surface of cells. These molecules include insulin receptors, transferrin receptors, lactoferrin receptors, and low-density lipoprotein receptor-related protein-1 [49].

5. Nanomedicine for ischemic stroke

In this section we summarize relevant nanomaterials and their corresponding drug-loading strategies or modification methods as tools to develop new therapies. Similarly, we summarize their advantages and existing shortcomings. Please see Tables 1 and 2.

5.1. Liposome

Liposomes are synthetic spherical cells composed of single amphiphilic lipid bilayers (Fig. 4) [67–71] that have been widely used as drug delivery systems to improve the safety and effectiveness of therapeutic molecules, such as drugs, nucleic acids, vaccines, and proteins [72–76].

The application of liposomes in the treatment of stroke has been widely studied because they have the ability to cross the BBB and stay in the blood stream for a relatively long time. As a result, they can deliver enough therapeutic drugs to brain tissue [77]. Imaizumi et al. studied the role of liposomes as precursors in the treatment of focal ischemic stroke. With short half-life and inability to pass the blood-brain barrier, superoxide dismutase (SOD), a free radical scavenger, is administered through the jugular vein in the form of an encapsulated liposome. An animal model study showed augmented levels of SOD and decreased infarct volume [50]. In addition, the circulation time of liposomes can be prolonged through modification of their surface by polyethylene glycol (PEG) [52]. The accumulation of PEGylated liposomes in ischemic brain has been measured [78], attributed to disruption of the BBB, heightened vesicle infiltration and long accumulation at the ischemic site. Evidence shows that in middle cerebral artery occlusion (MCAO) rat model, a

Table 1
List of nanomaterials/strategies for ischemic stroke therapy.

Nanomaterials	Strategies	Major findings
Liposome	Encapsulation of superoxide dismutase	Animal models using liposome agents showed augmented levels of superoxide dismutase (SOD) and decreased infarct volume [50]
	Changing Surface Charge	The absorption rate in ischemic area is higher [51]
	PEGylation	The circulation time of liposomes can be prolonged and can accumulate in ischemic brain area [52]
	Bind specific ligands to the surface of liposomes	Liposomes could effectively reach the brain injury area, and significantly decrease infarct volume and neurological deficit following middle cerebral artery occlusion [53]
Polymeric nanoparticles	Loaded with Z-DEVD-FMK	Showed significant decrease in nerve injury, caspase-3 activity and reduced infarct volume [54]
	Cationic polymer micelles	High efficiency, safe and reliable for tracing stem cells in vivo using magnetic resonance imaging [55]
Metal nanoparticles	BBB permeation mediated by external magnetic field	Under the external magnetic field, metal nanoparticles showed accumulation a perivascular zone of the brain parenchyma and on-demand drug release [56]
	MRI-monitored magnetic targeting	Magnetic targeting induced a 5-fold increase in the total glioma exposure to magnetic nanoparticles over non-targeted tumors [57]
	Free radical scavenging by autocatalytic	Cerium oxide nanoparticles show a significant neuroprotective effect on adult rat spinal cord neurons [57]
	Free radical scavenging	Cerium and yttrium oxide nanoparticles may be used as effective agents in prevention and possibly treatment of diabetic neuropathy [58]
Carbon nanotubes	chemical bonding of amine groups on the surface	Aminemodified single-walled carbon nanotubes protected the brains of treated rats from ischaemic injury [59]
Graphene	Adsorption of ruthenium carbonyl clusters	Commodified GO can be used for CO-mediated vasodilatory treatment [60]
	Modification with poly (amidoamine) dendrimer-grafted gadolinium	The modified GO be used as a contrast agent for magnetic resonance imaging to identify the location and extent of blood-brain barrier opening and quantitate drug [61]
	Modification with PEG	The PEGylation of rGO did not improve interaction with components of the BBB. In contrast, the attachment of PEG to rGO induced deleterious effects [62]
	matrix-assisted laser desorption/ionization mass spectrometry imaging	rGO systemically-injected was found mainly located in the thalamus and hippocampus of rats [63]
Black phosphorus	BBB permeability increased by NIR irradiation	BP nanosheets can selectively capture Cu ²⁺ and enhance the BBB permeability [64]
Hydrogels	Local injection of hydrogel	Effectively cross the blood-brain barrier, thereby promoting the infiltration of

Table 1 (continued)

Nanomaterials	Strategies	Major findings
		parenchyma cells around the scaffold and promoting local regeneration.
	Gelatin microspheres(GMS) loaded with osteopontin	Duration of osteopontin release was significantly extended [65]
Dendrimers	PEGylated poly(amido amine) (PAMAM)	Reduced blood clotting.
	Dexamethasone-conjugated polyamidoamine generation 2 (PAMAM G2-Dexa)	Efficiently delivered heme oxygenase-1 (HO-1) gene into the ischemic brain [66]

Table 2
List of the advantage and disadvantage for nanomaterials.

Nanomaterials	Advantages	Disadvantages
Liposome	High efficiency, low toxicity, long-term efficacy, ability to deliver both hydrophilic and lipophilic compounds [262]	Rapid systemic elimination, rapid metabolic degradation of phospholipids. Stability problems associated with long-term storage. Inability to provide sustained drug release. They are only moderately efficient for the encapsulation of lipophilic compounds [263–268]
Polymeric nanoparticles	the ability to modify drug release; increase the stability of volatile drug; incorporate into other activities related to drug delivery [269]	high cost; the preparation process is complex and the reproducibility is low
Metal nanoparticles	MRI and magnetic targeting performance; free radical scavenging	Potential toxicity associated with complex ingredients [270]
Carbon nanotubes	High penetration power and surface area; more than one molecule can be conjugated to their surface	Low biodegradability and dispersivity, possible induced oxidative stress and Lung disease [170,171]
Graphene	Polyaromatic structure and higher surface area	The lack of standardization; Difficult to biodegrade; Damage to the lungs [215,271]
Black phosphorus	Biodegradable; selectively capture Cu ²⁺ [64]	High cost; difficult to control shape and size
Hydrogels	Similar to the flexibility of natural tissue; PH or temperature sensitive; Biocompatible and biodegradable [272]	Thermosensitive hydrogel may cause excessive or insufficient drug release due to temperature stimulation [273].
Dendrimers	Easy surface modification; ability to interact with charged functional groups [274].	The specific toxicology, biocompatibility and in vivo distribution of various dendrimers need further in-depth study [274].

single injection of polyethylene glycol liposomes containing antiepileptic drug F506 at a low dose can significantly reduce infarct volume and improve motor function [79]. Other studies showed that nonpolyethylene glycol liposomes with different surface charges achieved early brain deposition following intratracheal cervical injection. The accumulation of these liposomes in the brain after intra-arterial injection is greater than that of cationic or neutral cationic vesicles, which may be due to the electrostatic interaction between cationic liposomes and negatively charged cell surface, and the absorption of nanoparticles is enhanced through the absorption of intercellular removal [80].

Another method to further improve drug transport across the BBB is to bind specific ligands to the surface of liposomes and target the surface proteins expressed on BBB. This strategy can increase the uptake of liposomes by BEC through receptor-mediated cell transport, thus leading to greater concentrations of the drug reaching the ischemic areas. It is reported that liposomes containing the neuroprotectant (ZL006) may be

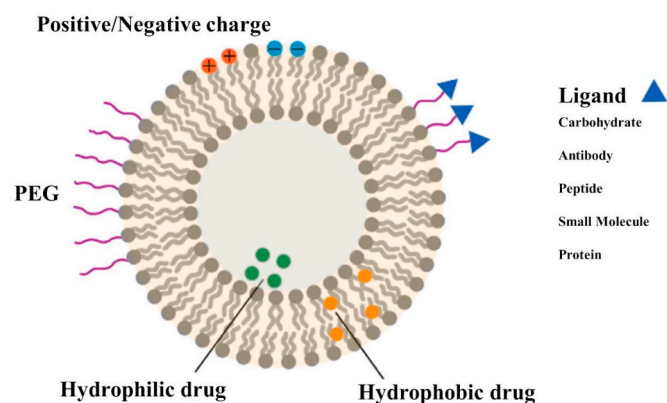


Fig. 4. Schematic diagram of different liposome membrane functionalization strategies. Reprinted with permission from Ref. [83]. Copyright 2019 PERGAMON-ELSEVIER.

a double target therapeutic strategy for ischemic stroke [81]. HSP72 (heat shock protein 72) is used as a target protein specifically expressed in the ischemic area around the infarct. PEGylated liposome with cytosine as carrier combined with HSP72 antibody can selectively aggregate in the ischemic area following a middle cerebral artery occlusion and increase the beneficial effect of drugs [82]. When other neuroprotective drugs such as VEGF (vascular endothelial growth factor) were loaded into liposomes and immune-targeted at the ischemic region, the same promising results were observed. The liposomes could effectively reach the brain injury area, and significantly reduce infarct volume and neurological deficits [53]. The surface of liposomes was modified with a transferrin receptor derived peptide ligand (T7) that improving the permeability of the BBB and a stroke-homing peptide (SHp) that targeting the ischemic areas. As a result, T7&SHp-P-L/ZL006 liposomes reduced the neurological deficit, infarct size, and histopathological changes in the MCAO rat model [81].

In general, liposomes have good drug loading capacity, drug protection ability, and high biocompatibility. However, its use in the treatment of stroke has the disadvantage of low targeting. Studies have demonstrated that the brain targeting ability of liposomes can be improved by conjugating PEG, changing the surface charge, or by conjugating specific targeting ligands, thus enhancing the therapeutic effect.

5.2. Nanoparticles

5.2.1. Polymeric nanoparticles

Biodegradable polymeric nanoparticles have been studied as drug delivery platforms because of their high biocompatibility and good sustained-release profiles [84–88]. There are clinical trials of polymer nanoparticles for anticancer and oral antimicrobial adjuvants [89,90]. Poly(D, L-lactide-co-glycolide acid) (PLGA) was observed to be one of the most extensively used to create nanoparticles for stroke. Mdzinarishvili et al. used glutathione-coated PLGA-b-PEG NPs to delivery thyroid hormones (T3) to promote neuroprotection to ischemic brain [91]. The neuroprotective effect of T3 was markedly lower compared to T3 in the PLGA-PEG formulations [91]. Although polymeric nanoparticles are promising options for targeted drug delivery, there are limitations that include high cost and complex manufacturing [92].

Polymeric nanoparticles can carry hydrophilic reagents and they can internalize drugs into cells via endocytosis. In one study, PLGA nanoparticles were encapsulated in balloon-expandable stents by a hydrophilic dye, fluorescein isothiocyanate (FITC). When coronary smooth muscle was co-incubated with FITC, the effective transmission of Polymeric NPs encapsulated by FITC was observed [93]. Cationic polymer micelles with neural stem cell labeling capabilities were designed recently. It has been shown that the micelles have high efficiency, safety

and reliability in tracing stem cells in vivo using magnetic resonance imaging [55]. In other studies, polymersomes have been developed to form a polymeric NP for the application of therapeutic stem cell MRI image analysis in stroke patients. In addition to polymersome nanospheres are also a key component of NP [94] because of their large surface area and neuroprotective properties. Nanospheres loaded with Z-DEVD-FMK showed significant alleviation of nerve injury, caspase-3 activity and reduced infarct volume, which may help treat stroke [54].

Nanoparticles possess excellent drug delivery properties, which can improve drug targeting efficiency and may be useful for controlled drug release. A number types of nanoparticles have been used as drug delivery carriers to cross the BBB since they can avoid phagocytosis by the reticuloendothelial system (Fig. 5), and increase the concentration of drugs in brain [95].

5.2.2. Metal nanoparticles

Metal nanoparticles also show great potential for the treatment and detection of brain diseases [97–101]. The shape and size of metal nanoparticles are uniform and easy to control during synthesis, which would allow them to meet quality control requirements for clinical application [28,102–105]. With unique surface plasmon resonance characteristics [106–110], metal nanoparticles not only have enhanced photothermal capability, but they also have excellent imaging and detection performance. Since some metal nanoparticles are magnetic [111–114], they can be used for magnetic hyperthermia, magnetic targeting, and magnetic resonance imaging (MRI) [115–118]. The surface of metal nanoparticles are also easy to modify, which is a prerequisite for the application of drug delivery platform. Chertok et al. [57] successfully used magnetic fields to target iron oxide nanoparticles with a hydrodynamic diameter of 110 ± 22 nm to brain lesions. Iron oxide nanoparticles have superparamagnetic behavior, which can protect materials from self-aggregation when there is no external magnetic field. In vivo experiments have demonstrated that effective magnetic targeting can be achieved by placing the head of the rat between the poles of an electromagnet. For this, magnetic field densities of 0.4 T were used to demonstrate enhanced (by 500%) iron oxide nanoparticles accumulation in. Kong et al. [56] utilized a modified emulsion process to obtain iron oxide particles with significantly improved magnetization and uniform particle size (~ 100 nm). Experimental evidence of BBB transport is shown in Fig. 8 B1–B5. After implantation of the Nd-Fe-B magnet, the right hemisphere of the mouse brain exhibited a much stronger nanoparticle enrichment than the untreated sample (left hemisphere), indicating effective magnetic targeting. Further non-invasive experiments have shown that magnets placed outside the head of the mouse can also effectively guide the enrichment of nanoparticles into the brain (25-fold improvement compared to the control group). After exposure to the magnetic field, the nanoparticles entered the peripheral space and parenchyma from capillaries. It is worth noting that the nanoparticles can penetrate the BBB under a magnetic field without damaging BBB integrity. Atomic force microscopy images show that nanomaterials can efficiently accumulate in human endothelial cells (>800 nm), indicating that endothelial cell membrane-mediated translocation may be the mechanism involved in the process. After targeting brain, an external magnetic field can effectively control the release of the nanoparticles-based drug delivery platform.

The use of nanoparticles in the treatment of stroke is not limited to drug delivery system. Studies have indicated that some specific metallic nanoparticles can act as scavengers of ROS. Platinum nanoparticles displayed antioxidant effect by scavenging superoxide anions and hydrogen peroxide in an in vivo test system. Cerium oxide nanoparticles were also used as ROS scavengers to reduce oxidation and provide neuroprotection to rat spinal cord neurons [119]. A recent study indicated that cerium oxide nanoparticles increased the survival of undifferentiated PC12 cells under oxidative stress. Cerium oxide nanoparticle pre-treatment decreased ROS production, proteins expression of LPO, Bax and caspase-3 [120]. These findings suggest that Cerium oxide

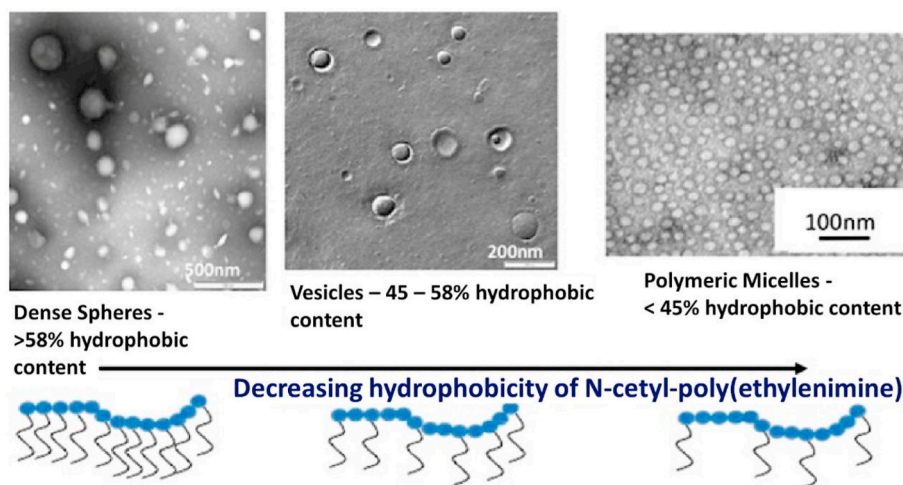


Fig. 5. Polymeric nanoparticles, polymeric vesicles and polymeric micelles all formed from various cetyl poly(ethylenimine) amphiphiles. Reprinted with permission from Ref. [96]. Copyright 2013 Springer Science+Business Media New York.

nanoparticles can be used as a therapeutic agent against oxidative stress and apoptosis. After years of development, some metal nanoparticles have achieved clinical application. For example, iron oxide-based MRI contrast agents have been clinically approved in Europe and the United States, and human trials of photothermal therapy based upon gold nanoparticles have also been reported [57,121–125].

5.2.3. Carbon nanotubes

Carbon nanotubes are a class of nanomaterials, composed of graphite sheets tubes with nanometer diameters [126–131]. They exhibit single- or multi-walled structures, characterized by open ends or closed with fullerene caps (Fig. 6) [132–137]. With unique structures, excellent electrical, mechanical, optical and thermal properties and high specific surface area, carbon nanotubes (CNTs) have great application in various fields [138–145]. Their main medical applications include drugs, tissue engineering, biosensor, gene therapy, hormone and enzyme delivery [146–150]. CNTs have been used in non-carrier systems due to the possibility of functionalization of their physical and biological properties using specific chemical components [151]. As the BBB cannot be penetrated through passive diffusion, the conjugation of compounds that promote the active transport to the brain is essential for emerging applications in nanomedicine. In the last two decades, they have gained a great attention as nanocarrier systems considering the unique property of carbon nanotubes [152]. With high specific surface area, they can effectively bind different molecules [153–158], and their properties can be manipulated by functionalization with chemical compounds to further improve their physical and biological properties [159–163].

Due to the numerous advantages mentioned above, the application of carbon nanotubes in brain diseases has received some attention. As a

prerequisite for clinical application, fluorescently labeled multi-walled carbon nanotubes have been found to penetrate microvascular cerebral endothelial monolayers without significant toxicity to cerebral endothelial cells [164]. Another research group also obtained similar results by ^{111}In labeling method, Raman microscope and multiphoton luminescence microscope image [165]. Excellent BBB penetration distinguishes carbon nanotubes from common drug carriers. You et al. [166] designed dual-targeted carbon nanotubes as a drug delivery platform against orthotopic glioma. Compared with free oxaliplatin, the oxaliplatin drug-loading platform based upon carbon nanotubes shows significantly improved BBB permeability. In addition, a recent study showed that carbon nanotubes can be used in nanofiber scaffolds, which can significantly improve neuronal growth and differentiation, indicating potential application in the field of peripheral nerve restoration [167]. After modification, multi-walled carbon nanotubes (f-MWCNTs) were co-incubated with an *in vitro* BBB model. Because of energy-dependent transcytosis, f-MWCNTs effectively penetrated cell monolayers. Amine-modified single-walled carbon nanotubes have also been shown to provide neuroprotection to rats following MCAO, and benefit behavioral functions [59]. Although carbon nanotubes have many benefits, there are limitations to their use, including poor solubility in water, low biodegradability and dispersivity, and deleterious drug-induced oxidative stress and lung disease [168–170].

5.2.4. Graphene

Graphene is another recently discovered nanomaterial with interesting properties. With the quantum confinement effect caused by ultrathin thickness, graphene exhibits novel performance in electrons [172–176], thermal [42,177–180] and optical properties [181–186], and is widely used in laser [184,187–190], sensing [191–195], optoelectronic devices [196–198], biomedicine [31,199–203] and other fields. The atomic thickness determines the extremely large specific surface area of graphene [188,204–207], which makes it suitable as a drug carrier. It is also very sensitive to the action of photons [208–211], so it has a good performance profile in the field of light-controlled drug release and photothermal therapy, which can improve the permeability of BBB. The delocalized π -electrons of graphene are advantageous for binding various aromatic ring containing drug molecules through π - π stacking. As an important member of the graphene family, graphene oxide (GO) and reduced graphene oxide (r-GO) have a rich oxygen-containing group on the surface, which ensures water dispersibility and easy modification. Considering the above advantages, researchers have used graphene as a drug carrier to cross the BBB. Yang et al. [61] synthesized graphene oxide with a single layer thickness and

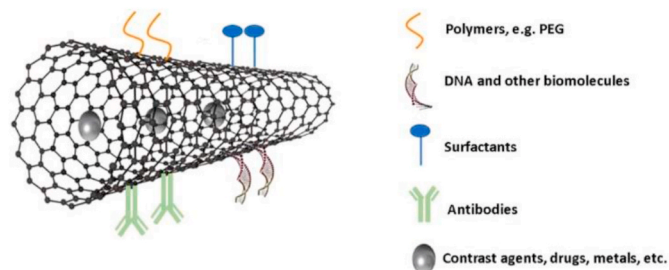


Fig. 6. Schematic diagram of preparation of PEG-MWCNTs (multiwalled carbon nanotubes) Reprinted with permission from ref[171]. Copyright 2018 MDPI.

size range of 100–300 nm via the modified Hummers' method. It can be suspended in water for several months due to the oxygen-containing groups enriched on the surface. Transcription activator peptide as well as methoxy polyethylene glycol were used to modify the surface of GO to further improve blood circulation stability and BBB penetration. GO exhibits significant broadband absorption in the near-infrared region, which is beneficial for photoacoustic imaging. In vivo experiments confirmed that drug-loaded functionalized GO was able to efficiently aggregate in mouse brain, while the control group (pure GO) was almost incapable of penetrating the blood-brain barrier. The functionalized GO drug delivery platform enables a safe combination of treatment and rapid detection compared to simple drugs.

A study of PEG-modified rGO showed significant toxicity to primary rat astrocytes, while unmodified rGO showed negligible toxicity [62]. Astrocytes treated with PEG-rGO and rGO resulted in completely different immunofluorescence images. The former shows a complete lack of normal cellular structure, loss of contact between cells, and a marked decrease in the number of cells while the latter exhibits only moderate levels of cell body and process retraction. Similar results were obtained from in vitro experiments with rat brain endothelial cells as the study model.

In vivo experiments have shown that PEG-rGO triggers a significant and sustained down-regulation of BBB-associated proteins compared to rGO. Further experiments confirmed that PEG-rGO can induce greater levels of ROS in cells than rGO, which may be a source of PEG-rGO toxicity. It is worth noting that the sizes of rGO and PEG-rGO used in this work are 342 ± 23.5 nm and 910 ± 32.7 nm, respectively, which are much larger than those commonly used in biological applications, and may be the reason of significant differences.

Few studies have suggested that GO can be applied to the treatment of stroke.

Because of the transient decrease of the BBB's paracellular tightness, rGO can reach the hippocampus area through blood circulation following ischemia [212]. rGO-induced transient opening of BBB did not show significant deleterious effects. Due to the ability of rGO to temporarily increase permeability of BBB, drug delivery to the lesion site can be measured (Fig. 7) [213]. Improved BBB permeability after using rGO indicates the great potential of graphene group materials in brain diseases.

A recent study developed a facile CO-release platform based on the size-dependent adsorption properties of ruthenium carbonyl clusters (Ru-carbon monoxide (CO)) onto graphene oxide (GO) for treatment of stroke, as shown in Fig. 8 A1-A6. Photothermal therapy induced oxidation of RuII(CO)₂ to RuO₂ on the GO surface, leading to the release of CO. A cortical photothrombotic ischemia (PTI) rat model was used to

demonstrate vasodilation and stroke protective effect of the RuO₂/RuII(CO)₂/6Ru-CO-GO composite. The results suggested that infarct volume was decreased in the group treated with RuO₂/RuII(CO)₂/6Ru-CO-GO composite [33]. Advances are promising, but there are still many important problems to be resolved before clinical application. First, the graphene product family includes GO, rGO and graphene nanosheets, which have very different characteristics. A standardization protocol to distinguish and characterize different molecules has not been developed [214]. In addition, poor degradation of the graphene family in vivo also needs to be improved. Although some work has shown that most of the graphene can be metabolized out of the body through urine, a small but significant amount of graphene will still remain in organs for more than 270 days [215].

5.2.5. Black phosphorus

With unique structure and properties, black phosphorus (BP), namely phosphorene, is becoming an important molecule [216–220]. BP has a broadband-adjustable direct band gap, which ensures that it has a broad spectrum of intense light absorption [5,218,221–224,224–228]. BP exhibits a high extinction coefficient in the near-infrared region, optimal photothermal conversion efficiency and attractive fluorescence quantum yield, thus has application in the field of photothermal therapy, photoacoustic imaging and fluorescence imaging, etc. [34, 229–231].

Sun et al. [232] used a simple liquid phase exfoliation method to prepare BP quantum dots (BPQDs) with an average size of 2.6 ± 1.8 nm, which can be quickly cleared by the kidneys to avoid possible long-term toxicity. Cell experiments have shown that ultra-small BPQDs have effective photothermal killing effects and great biocompatibility. PEG modification on the surface of the BPQDs enhances the stability and dispersion under physiological conditions. BPQDs coated with PEG were prepared via a one-pot method using red phosphorus as a raw material. The photoacoustic signal intensity of the BPQDs increases linearly with increasing concentration (in the range of 0–250 mg/mL). In vivo experiments have also confirmed the excellent photoacoustic imaging capabilities of BPQDs. BP also shows intense blue light emission, indicating the potential for bioluminescent imaging. Lee et al. [233] obtained BPQDs with great biocompatibility and water dispersibility via liquid phase exfoliation in chloroform. BPQDs exhibits the maximum fluorescence at 437 nm under the excitation of 377 nm, which may be derived from the band gap transitions in the cases of chloroform and DMAc or the radiative recombination of the surface-confined electrons and holes in the case of pyridine. Further experiments have shown that BPQDs have a high quantum yield (~5%) and significant fluorescence characteristics as well as negligible toxicity in cells. The ultrathin

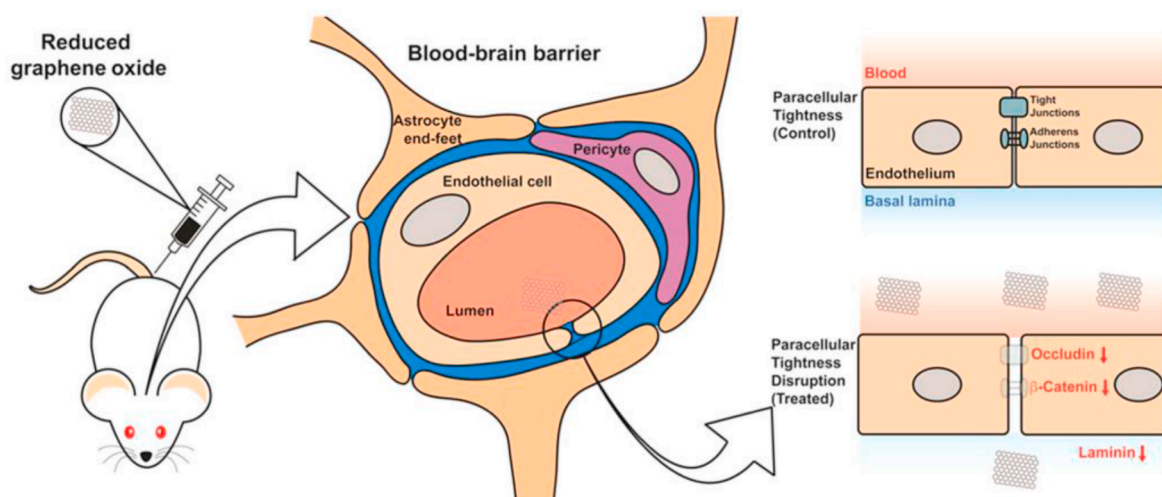


Fig. 7. Schematic diagram of rGO opening BBB. Reprinted with permission from ref. [63] Copyright 2015 BMC.

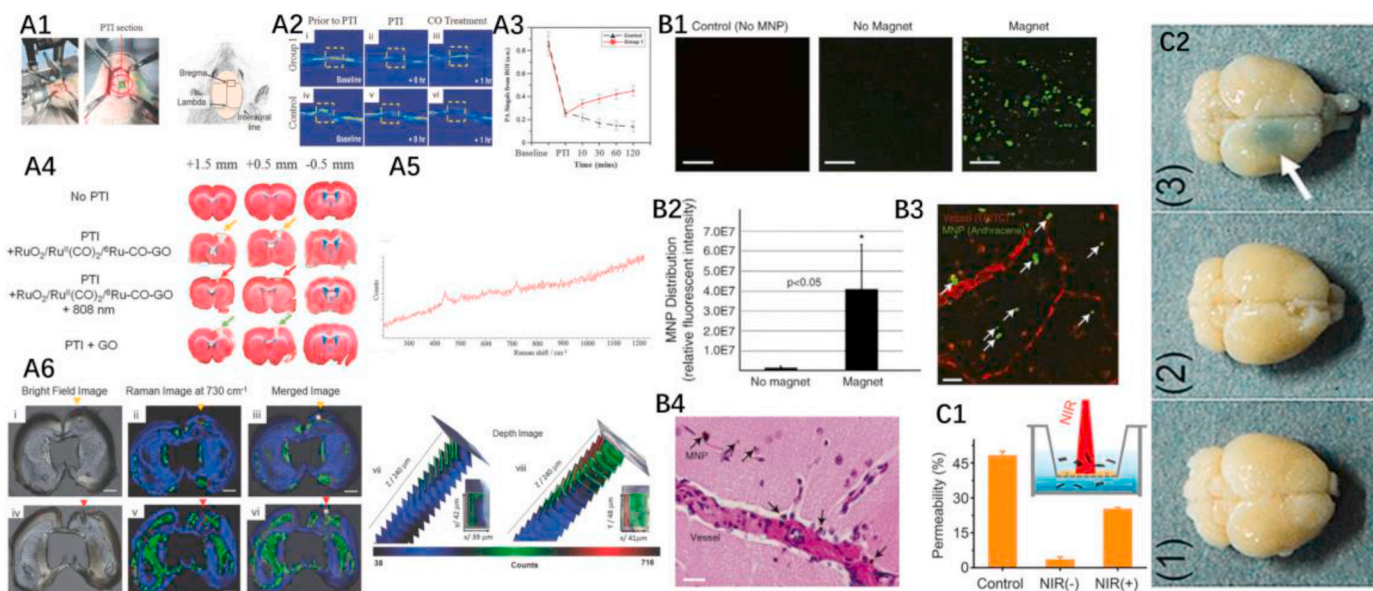


Fig. 8. A1–A6. The therapeutic performance of GO-based drugs on stroke. (A1) Experimental setup. (A2) Photoacoustic vessel cross-section images of vasodilatation under irradiation with an 808 nm laser in a PTI rat treated with (i–iii) Ru–CO–GO (group 1) and (iv–vi) GO (control). The enhanced photoacoustic signal of the experimental group indicates that the released CO can effectively promote vasodilation. (A3) The intensity of photoacoustic signals of group 1 and control at different time points indicated the rapid therapeutic. (A4) The infarct volume of 1 mm coronal brain sections of rats at +1.5 to –0.5 mm to the Bregma, by TTC staining. (A5) Raman spectroscopy of brain slides. (A6) Raman imaging of brain slides (+0.5 mm) (i–iii and vii) Ru–CO–GO and (iv–vi and viii) GO. Scale bar: 0.4 cm. Reprinted with permission from ref. [244]. Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. *Region of depth scan. (B1–B4): BBB crossing of magnetic nanoparticles in the magnetic field. (B1) Images of mouse brain sections treated without magnetic nanoparticles (left); with magnetic field, but without magnetic nanoparticles (middle); with magnetic fields and magnetic nanoparticles (right). Scale bar, 20 μ m (B2) Relative fluorescence intensity of brain sections in B1. The enrichment of magnetic nanoparticles increased 26-fold after the treatment with the magnetic field. (B3) Confocal image of extravasation of magnetic nanoparticles in the vessels. Scale bar, 50 μ m (B4) Image of brain sections showing aggregation of magnetic nanoparticles around blood vessels. Scale bar, 20 μ m. Reprinted with permission from ref [56]. Copyright 2012 PERGAMON-ELSEVIER. (C1–C2): In vitro and in vivo BBB penetration of BP. (C1) bEnd.3 cell monolayer was seeded in transwells to obtain an in vitro BBB model, as shown in the inset. 48% of BP was transported from the upper chamber to the lower chamber in the control group (no bEnd.3 cell). With bEnd.3 cell monolayer, only 3.5% of BP spontaneously traversed to the lower chamber, while the delivery of BP was increased by 6-fold under the illumination. (C2) The images of mouse brains with Evans blue staining show obvious BBB crossing ability of BP under the irradiation. (1) BP (2) NIR, (3) BP + NIR. Reprinted with permission from ref [64]. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

thickness and unique puckered lattice configuration [207,223,234,235], allow BP nanosheets to be used as a drug platform. Tao et al. [35] found that BP has drug-loading ratios tested to be 108%, higher than traditional materials. After loading of drugs, targeting molecules and fluorescent molecules, BP nanosheets achieved targeted detection-therapeutic combined performance and light-controlled drug release capabilities. In addition to its excellent therapeutic and detection capabilities, the most important feature of BP is its complete biodegradation under physiological conditions [236]. BP can degrade into phosphate [237–241], which is a ubiquitous metabolite in body. Illumination and modification can effectively control the degradation rate from 1 h to one month, indicating the potential of BP as the next generation of an intelligent drug-loading platform.

2D BP nanosheets can be used as a robust nanocaptor for Cu^{2+} and protect neuronal cells against Cu^{2+} induced neurotoxicity, as shown in Fig. 8C1 and C2. BP nanosheets displayed good BBB permeability under near-infrared irradiation because of their photothermal effect. Moreover, BP nanosheets decreased intracellular ROS content and increased mitochondrial membrane potential (MMP). BP nanosheets have excellent biocompatibility and stability in vitro and in vivo. Therefore, BP could be regarded as a promising neuroprotective drug delivery system [38]. The biodegradability of BP distinguishes it from traditional inorganic nanomaterials. However, balancing the biodegradability and blood circulation time is still a key factor to achieve effective treatment. In addition, the 2D BP discovered in 2014 is so young that some of the consequences of its exposure to biological environments are still unclear [242]. For example, studies have shown that phosphate anions produced by the rapid degradation of BP can kill cancer cells, which also arouses

concerns about the side effects of BP degradation products to normal cells [243].

5.3. Hydrogels

Recent efforts have focused on engineered injectable hydrogels that can be directly transplanted in the stroke cavity. In situ injectable hydrogel materials provide a unique platform to bioengineer repair environments at the stroke site. The hydrogels can be produced to match the mechanical properties of the normal brain by modulating the crosslinking density. Hydrogels promote repair by offering structural support to the injured tissue, leading to minimized secondary cell death (Fig. 9).

Local injection of hydrogels can effectively bypass the blood-brain barrier, thereby promoting the infiltration of parenchyma cells around the scaffold and promoting local regeneration. Injectable hydrogels can also be used as cell transplantation carriers to transport neural progenitor cells. Since invasive delivery is required to enter the brain and skull, direct delivery of cells to the brain after stroke along with hydrogel biomaterials must be controlled so that adjacent tissues are not damaged [245]. Ideally, the injection should be guided by non-invasive imaging [246]. Mado et al. have successfully used magnetic resonance imaging to guide hydrogel injection and drainage of the brain at the same time to prevent the accumulation of intracranial pressure [247]. Currently, hydrogels are used for manufacturing contact lenses, hygiene products, tissue engineering scaffolds, drug delivery systems, wound dressings [248], and as antimicrobial agents [249].

Hydrogels can be used as drug carriers loaded with anti-

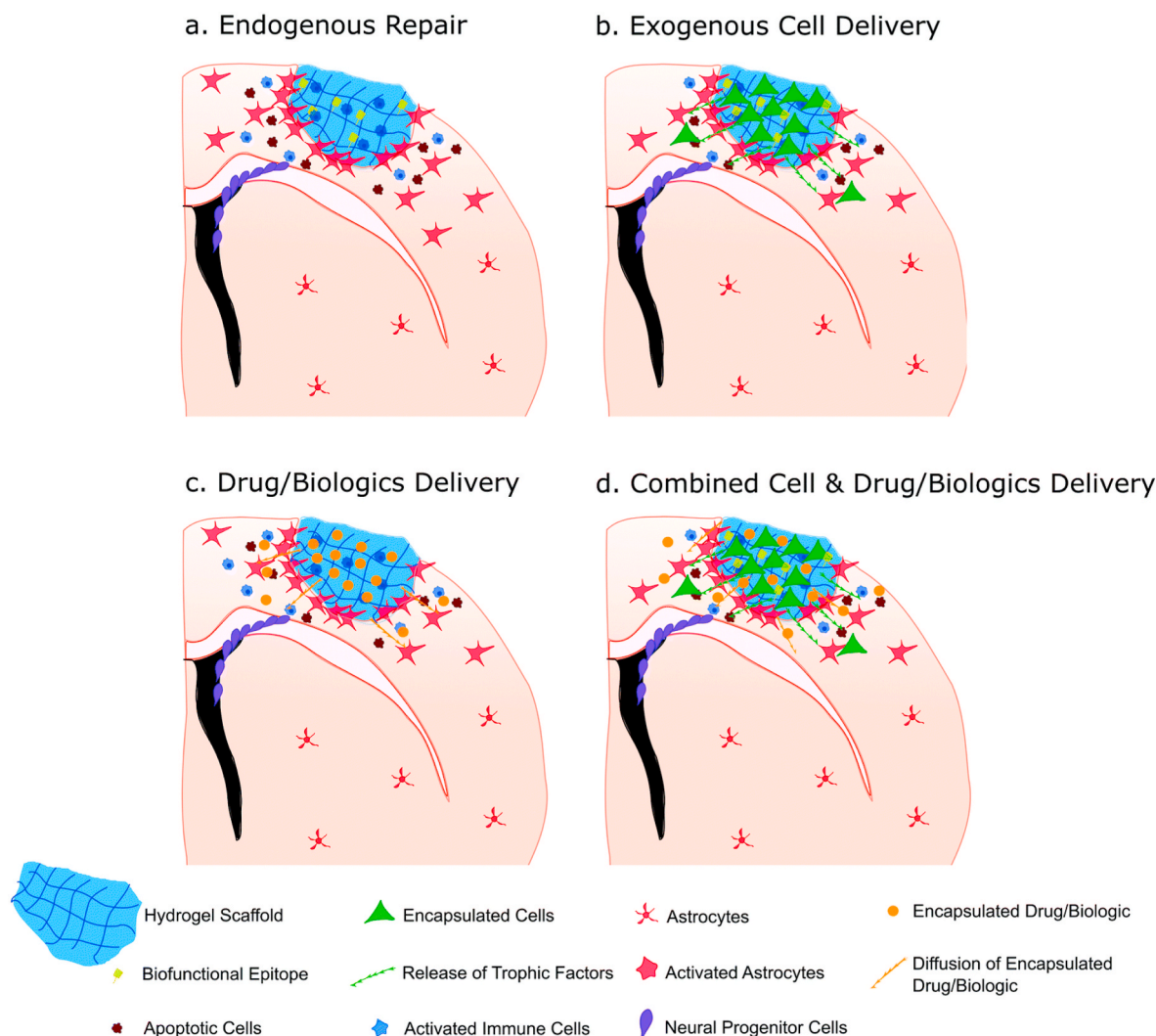


Fig. 9. The potential application of injectable hydrogels in stroke treatment. (a) injecting bio functional hydrogels into infarcted areas can induce endogenous repair mechanisms, such as angiogenesis and neurogenesis. (b) injectable hydrogel can be used as a cell delivery carrier to provide a three-dimensional environment in the infarcted area. Then, coated exogenous cells can release therapeutic nutrients to the surrounding environment to help regeneration. (c) injectable hydrogel can be used as a reservoir for drug/biological agents in the infarct area for controlled and sustained administration. The goal of promoting regeneration includes increasing neural precursor cell migration from the SVZ, reducing inflammation and attenuating the immune response. (d) It may also be a dual function method to combine the delivery of exogenous cells and drug/biological agents. Reprinted with permission from Ref. [254]. Copyright 2019 ROYAL SOC CHEMISTRY.

inflammatory drugs to improve bioavailability. Gelatin microspheres (GMS) loaded with osteopontin were injected into a mouse following a stroke. After encapsulation with GMS, the duration of osteopontin release was significantly extended [65]. Delivery from the microspheres showed increased neuroprotection, and decreased inflammation after stroke. Hydrogel can be applied to achieve sustained and sequential delivery of epidermal growth factor (EGF) [250], erythropoietin [251, 252], and cyclosporine A [253]. These results indicated improved tissue repair and reduced stroke-induced damage when compared to the delivery of the same drugs via traditional bolus delivery in the brain.

5.4. Dendrimers

Dendrimers are a class of synthetic macromolecule that present a tree-like topology and specific encapsulation properties. Dendrimers have interesting structural features, including globular and layers of branched nanostructure, and several terminal functional groups on the outside layer. They have the ability to form complexes and encapsulate a variety of molecular [255]. These polymer-based nanostructures are widely used as nanocarriers to transport various therapeutic and

imaging agents because polyamidoamine, polypropylenimine, and polyaryl ether are used in dendrimer formulations and they can encapsulate both hydrophilic and hydrophobic molecules [256,257]. Dendritic macromolecules are widely used in the treatment of central nervous system diseases as their ability to transverse the blood-brain barrier [258]. In addition, they have the ability to cross various membrane or biological barriers through endocytosis-mediated cellular internalization.

In a recent study, the biocompatibility of cationic poly(amido amine) (PAMAM) dendrimers was significantly increased by PEGylation as a degree of functionalization [259]. The PEGylated PAMAM dendrimers did not influence the integrity of the BBB in an in vitro model, nor did it show cytotoxicity in an in vitro hypoxia model induced by oxygen-glucose deprivation. Interestingly, the PEGylated dendrimers reduced blood clotting, which provided an additional beneficial function in the treatment of stroke. Further, optimized PAMAM formulation could be detected in the brain 24 h after administration in a permanent focal brain ischemia mouse model. The PEGylated PAMAM dendrimers prolong blood circulation half-life and have the potential for application in drug delivery system. In another study, dexamethasone-conjugated

polyamidoamine generation 2 (PAMAM G2-Dexa) efficiently delivered the heme oxygenase-1 (HO-1) gene into the ischemic brain [66]. e-PAM-R, a biodegradable arginine ester of PAMAM dendrimer, provided an efficient means of transfecting High mobility group box-1 (HMGB1) siRNA into primary neuronal cells and in the post-ischemic brain [260]. Starpharma has developed a dendrimer based product ‘vivagel’, which is designed to be used as an antiviral agent in the vagina and has successfully completed phase I clinical trials [261].

6. Conclusion and perspectives

Traditional drug therapy for ischemic stroke has limitations, and drugs need to penetrate the BBB to reach the ischemic region to achieve therapeutic effect. BBB is a barrier between the nervous system and other parts of the body, which can protect the brain from harmful stimulation. However, nanomedicines, such as liposomes, nanoparticles and hydrogels display great versatility regarding morphology, and surface physicochemical properties. They can effectively cross the BBB and deliver drugs to the lesion, reaching areas that are difficult to reach by conventional drugs. Nanomedicines are important molecules to be applied to treating stroke, based upon their ability to cross the BBB, transiently decrease the BBB paracellular tightness, and act as antioxidants. Nanomedicines can be actively transported by transcytosis, thereby improving BBB transport and improving drug permeability.

Considering that nanomedicines are not naturally existing in the human body, studies are mandatory to evaluate the bio-distribution and toxicological effects of these nanomedicines after systemic administration. Currently, there is little information regarding the pharmacological effects and interaction of nanomedicines with the human brain. According to the relevant literature, only 3 positive phase III randomized clinical trials (RCTs) in acute ischemic stroke were all reperfusion therapy. They are (National Institutes of Neurological Disorders and Stroke) (NINDS) validates the clinical effect of intravenous (IV) tPA for acute ischemic stroke within 3 h; Prolyse in Acute Cerebral Thromboembolism (PROACT) II demonstrated efficacy of IV tPA in selected patients out to 4.5 h; European Cooperative Acute Stroke Study (ECASS III) demonstrated the clinical and recanalization effect of intra-arterial (IA) prourokinase in the treatment of M1 or M2 middle cerebral artery occlusion within 6 h after stroke. Meanwhile, as a result of recruitment of RCTs for acute stroke is often difficult, it is hard to have sufficient samples to support the conduct of clinical trials. At present, because of such great challenges, such as the extremely short therapeutic window and the issue of stroke heterogeneity, there are no mature nanomaterials for acute cerebral ischemic stroke reported [275]. Animals and clinical studies investigating the toxic effects of nanomedicines on brain are limited. According to recent studies, carbon nanotubes have related toxicity in animal models [276], while liposomes, and hydrogels have limited negative effects [277]. Neurotoxicity of nanomedicines can originate not only from the core structure, but from their surface functionalization for active delivery. Although surface functionalization, such as surfactants and peptides can promote drug delivery via BBB permeability, it may also increase the risk of promoting toxic substance transport into the brain.

Nanomedicines are at an early stage of development and more in-depth research studies are needed to successfully translate these drugs to treat cerebral ischemia. Further investigations should be pursued to reveal the fate of nanomedicines after brain delivery and the potential side effects to offer more insight on translation from preclinical to clinical applications.

Declaration of competing interest

NO Conflict of Interest.

Acknowledgements

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