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Drug Delivery to the Brain across the Blood–Brain Barrier Using Nanomaterials

Yung-Hao Tsou, Xue-Qing Zhang, He Zhu, Sahla Syed, and Xiaoyang Xu**

A major obstacle facing brain diseases such as Alzheimer's disease, multiple sclerosis, brain tumors, and strokes is the blood–brain barrier (BBB). The BBB prevents the passage of certain molecules and pathogens from the circulatory system into the brain. Therefore, it is nearly impossible for therapeutic drugs to target the diseased cells without the assistance of carriers. Nanotechnology is an area of growing public interest; nanocarriers, such as polymer-based, lipid-based, and inorganic-based nanoparticles can be engineered in different sizes, shapes, and surface charges, and they can be modified with functional groups to enhance their penetration and targeting capabilities. Hence, understanding the interaction between nanomaterials and the BBB is crucial. In this Review, the components and properties of the BBB are revisited and the types of nanocarriers that are most commonly used for brain drug delivery are discussed. The properties of the nanocarriers and the factors that affect drug delivery across the BBB are elaborated upon in this review. Additionally, the most recent developments of nanoformulations and nonconventional drug delivery strategies are highlighted. Finally, challenges and considerations for the development of brain targeting nanomedicines are discussed. The overall objective is to broaden the understanding of the design and to develop nanomedicines for the treatment of brain diseases.

1. Introduction

Physiological barriers, such as the capillary endothelial barrier, intestinal barrier, cerebral spinal fluid barrier, blood-brain barrier (BBB), and many others defend against foreign substances and restrict the passage of certain molecules. The BBB, which controls the exchange of substances between the central nervous system (CNS) and the blood through a complex, dynamic, and adaptable interface, is the densest barrier in the human body and the primary protector of the CNS. The BBB is mainly formed by densely packed brain endothelial cells that result in tight junctions, and is surrounded by astrocytic endfeet, lumen, and pericyte cells (**Figure 1**A).[1] More specifically, the endothelial cells and tight junctions in the BBB create a restrictive network that prevents diffusion between cells. Pericytes, which are microvessels that wrap around the brain capillaries, help with BBB regulation and structural support and are distributed within close proximity to the endothelium.[2] Endothelial cells and pericytes are surrounded by the basal lamina and astrocytic perivascular endfeet, which provide support and anchoring to the BBB. Astrocytes maintain chemical stability and allow a cellular interaction with the neurons surrounding the BBB. These cells interact with the barrier and regulate the tight junctions, transporters, and enzyme systems. Astrocytic foot processes surround brain capillaries and facilitate induction of endothelial cells to form tight junctions during early development. They also secrete chemical agents that induce growth and differentiation of cells. During inflammation, perivascular macrophages and microglia can become activated and act as the brain's immune defense system.[3] This rigorous structure restricts the movement of external organisms and noxious chemicals across the BBB, thereby protecting the brain and allowing only select ions and molecules, such as O_2, CO_2, glucose, and ethanol, to pass via transport carriers. However, the BBB also inhibits the effective treatment of neurological diseases such as Alzheimer's disease (AD), strokes, gliomas, and Parkinson's disease by this same mechanism. Most molecules, including small molecular drugs and protein-based therapeutics necessary for the treatment of these diseases, cannot pass the BBB due to its highly selective semipermeable membrane nature, leading to the rapid and untreated progression of serious diseases.

There are a total of four different mechanisms by which substances pass through the BBB: simple diffusion, facilitated diffusion, simple diffusion through an aqueous channel, and active transport through a protein carrier associated with an active binding site.[4] Additionally, two types of diffusion, in terms transport routes, affect the uptake of materials across the BBB: transcellular diffusion and paracellular diffusion. Transcellular diffusion allows the transport of only hydrophobic substances across the phospholipid membrane of endothelial cells. Paracellular

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diffusion, which is restricted by tight junctions, involves the passage of small molecules across the barrier.[5] Modulation of the BBB is an important aspect of drug delivery. Opening of tight junctions and increased permeability were found under certain pathological conditions.[6] Receptors on the BBB that are capable of modulation have been studied and characterized.[7] Chemical agents such as adenosine triphosphate have been reported to influence the barrier via ligand–receptor interaction and endocytosis.[8] Changing the concentration of certain molecules can also affect the signal pathways and can mediate a range of physiological responses, allowing the endothelium to increase its uptake of specific drugs and molecules.[9]

Understanding the endothelial-astrocytic interaction in the BBB can aid in the treatment of diseases that cause BBB dysfunction and leakage. Steroids and other therapeutic agents have been found to help repair and improve BBB function, as well as increase permeability to allow drugs to cross from the blood into the brain.[10] While it has been found that BBB modulation can be orchestrated to allow for greater brain permeability, designing drug delivery systems that will allow major therapeutic molecules to cross into the brain still needs to be investigated further. On the other hand, successfully improving the delivery of therapeutics through functional nanomaterials is a revolutionary approach for the treatment of various diseases, such as cancers, infectious diseases, and many others. Several lipid and polymer-based nanomedicine formulations have been approved by the FDA for clinical use, including breast cancer and lung cancer treatments. In recent years, using nanocarriers in conjunction with therapeutics to improve drug delivery efficiency across the BBB has been gaining interest in the treatment of brain diseases. Nanomaterials, such as polymer-based, lipid-based, and inorganic-based nanocarriers are the best candidates for drug delivery systems (**Table 1**). Modification and optimization of certain variables such as size, ligand, and shape of nanocarriers lead to superior BBB penetration and targeting (Figure 1B).[11] The scope of this review is to provide an overview of the most recent nanotechnology developed for the treatment of CNS diseases as well as evaluate the strategies employed in influencing the BBB. The viability and efficacy of the administration routes of these nano-based delivery systems will also be discussed.

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2. Nanocarriers as Drug Delivery Systems

Nanotechnology is emerging powerful tool for the treatment of various diseases including cancer, cardiovascular, and infectious diseases.[12] A nanocarrier is a nanomaterial being used as a transport unit for another substance, such as a therapeutic agent. This form of delivery enhances the loading of poorly soluble drugs while increasing the bioavailability of the drug, thus improving the overall therapeutic efficacy. Generally, the transport of nanocarriers across the BBB for brain delivery occurs through the following mechanisms: (i) opening of tight junctions between endothelial cells or inducing local toxic effects, leading to localized permeabilization of the BBB and allowing the penetration of the drug/NPs; (ii) passing through endothelial cells via transcytosis; (iii) transporting through endothelial cells by endocytosis, by which content is released into the cell cytoplasm and then exocytosed in the endothelium abluminal side; or (iv) a combination of several of the aforementioned mechanisms (Figure 1C).Targeted drug delivery via nanocarriers is a promising alternative to the traditional methods of delivery. Conjugating surface ligands, such as targeting antibodies that correspond to the overexpressed proteins on the targeting site, onto the surface of nanocarriers allows for greater permeability and enhanced drug delivery via molecular recognition. NP-based delivery also allows for a time or stimuli-response, such as a pH-responsive or a temperature-responsive release of the encapsulated drug in a target location, rather than a sudden release.[13] Three types of drug delivery systems including polymer-based, lipid-based, and inorganic-based nanocarriers are discussed in this review.

2.1. Polymer-Based Nanocarriers

Polymers, including synthetic and natural polymers, were originally recognized for their potential drug delivery application

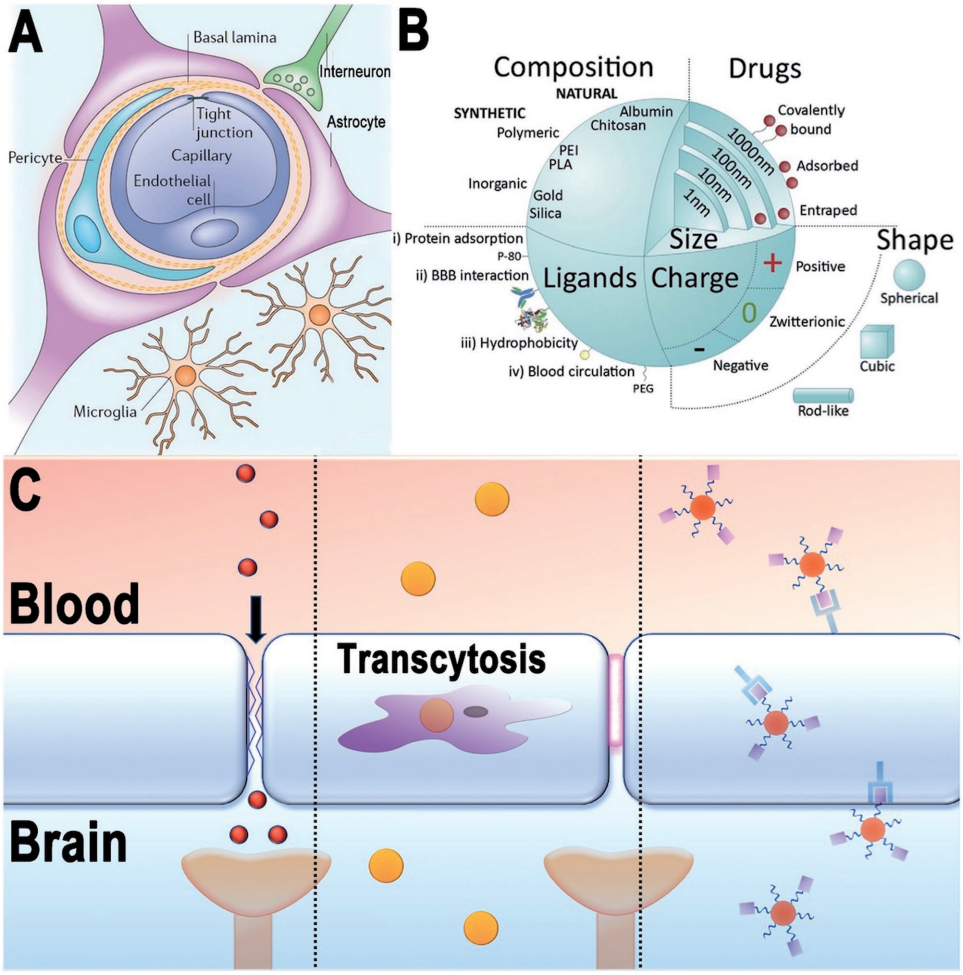

Figure 1. A) The schematic shows the structure of the BBB, which is formed by endothelial cells and surrounded by lamina and astrocytic perivascular endfeet. Pericytes and microglial cells are also presented.[1] B) The properties of nanocarriers such as type, charge, shape, among many others that affect the penetration and targeting of the BBB.[11] C) The various methods of transport of nanomaterials across the BBB for brain delivery. Reproduced with permission.[1] Copyright 2006, Nature Publishing Group. Reproduced with permission.[11] Copyright 2016, Elsevier.

in 1960s. Since then, polymers have been widely used in an impressive number of drug delivery products due to their favorable biocompatibility and biodegradability properties. Tremendous effort has been made to develop and optimize polymer-based nanomaterials, including polymeric NPs (PNPs) and polymer–drug conjugates, for specificity, improved bioavailability, reduced toxicity, and desirable pharmacokinetics.[14] Polymer-based nanocarriers can encapsulate and protect therapeutic drugs against enzymatic and hydrolytic degradation, and facilitate transport across epithelial barriers via passive or active delivery. It has been reported that polymeric nanocarriers loaded with drugs result in enhanced brain permeation, allowing for much higher concentrations of the drug in the target location and improving the overall efficacy of the drug.[15]

2.1.1. Polymeric NPs

The use of polymers to provide controlled and sustained delivery of therapeutics is a rapidly emerging field, and PNPs are some of the most extensively investigated polymeric drug delivery carriers. PNPs are usually synthesized from biodegradable and biocompatible polymers such as poly(D,L-lactide-*co*-glycolide) (PLGA), poly(lactic acid) (PLA), polyethylene glycol (PEG), poly(caprolactone) (PCL), poly(glutamic acid) (PGA), *N*-(2-hydroxypropyl)-methacrylate copolymers (HPMA), and poly(amino acids).[16] The polymer matrix-based NPs offer potentials in controlling the drug release profile and minimizing toxicity during polymer degradation through hydrolysis of ester linkages. Among these, PLGA NPs with an average diameter of 70 ± 19 nm, which are much smaller than conventional NPs, penetrated to volumes of ≈111 mm^3 when delivered in rat brains by convection-enhanced delivery, and ≈1180 mm^3 when delivered in pig brains.[17] Encapsulating dithiazanine iodide within these brain-penetrating NPs allowed for controlled drug release in the brain, significantly increasing survival in rats bearing brain cancer stem cells derived xenografts.

A recent study reported by Hanes and co-workers suggests that a dense PEG coating is needed to improve penetration of PNPs within brain tissues.[18] PEGylated NPs had a lower

Table 1. Formulations of nanomaterials for BBB delivery.

Type	Materials	Size [nm]	Charge [mv]	Ligand	Ref.
Polymer-based	heparin	63 ± 11 @ serum	−10 @ serum	SWL & cRGD	[95]
		164 ± 16 @ water	−30 @ water		
	ANG-PEG	92.7 ± 7.3	−3.35 ± 1.02	Angiopep-2	[96]
	DGDPT/pORF-hTRAIL	173 ± 5.6	6	T7	[97]
	PEG-PCL	88.4 ± 7.8	23.56 ± 0.96	Lf	[16b]
	PEG-PLA	111.30 ± 15.64	−24.3 ± 3.36	tLyp-1	[24]
	PEG-PLA	129.6 ± 2.1	−29.6 ± 3.6	Peptide-22	[62]
	PEG-PLA	107.45 ± 2.77	−21.33 ± 0.16	TGN & QSH	[67]
	DGL-PEG	90.6 ± 8.9	5.03 ± 0.8	LNP	[98]
	PEG-PMT	182.3 ± 3.4	10.4 ± 2.5	RVG	[99]
	PEG-PLA	125.5 ± 2.26	−29.33 ± 0.15	TGN & QSH	[23b]
	PBCA	≈140	−5 ≈ −3	PS-80	[69b]
	poly (ethylene imine)	117 ≈ 282	−6.9 ≈ 34	L-Glutathione	[100]
	PEI-PLL-PEG	≈165	≈ 20	Angiopep-2	[101]
	PEG-PLGA	95.78 ± 2.37	−34.5 ± 1.74	Pep-1	[102]
	DGLs-PEG	110	7.72 ± 2.80	RVG 29	[103]
	PAMAM-PEG	19		Tf & TAM	[104]
	PEG-PTMC	72		c(RGDyK)	[105]
	PEG-PTMC	≈71		2-deoxy-D-glucose	[69e]
	PEGGM-PDSGM	88.6 ± 1.2		Des-octanoyl ghrelin & folate	[69a]
	PLGA-CS	168 ≈ 177	19.6 ± 4.8		[16a]
	PGMA-MAL	190	−27		[106]
	PEG	20, 40, 100 & 500	−28.4 ± 3.2 @ 20 nm		[107]
			−9.2 ± 4 @ 40 nm		
			−22.4 ± 3.5@100 nm		
			−26.5 ± 2 @ 500 nm		
	PAA-PEG	62 ≈ 76	−7.5 ≈ −37		[19]
	PLGA	65 ± 16			[17]
	PDI-DSPE-mPEG$_{5000}$	48 ≈ 53			[108]
	TPETPAFN	10, 30 & 60			[57]
	PS	200 ± 0.01	−23 ≈ −60	IgG, Tf & ICAM	[75]
		501 ± 43.6 × 123.6 ± 13.3			
	PLGA-PEG	200	−30		[109]
	PEG	≈ 31		cRGD	[26]
	mPEG-b-PDPA	*D*: 21.3 ± 1.8		RGD	[25]
		L: 60 ≈ 600			
	PEG-PDMAEMA	80.3 ± 6.1	3.97 ± 1.44	TGN	[27]
Lipid-based	DSPE-PEG$_{2000}$	110 ≈ 120	≈ −11		[37]
	LEP-P85	3.8 ≈ 15		P85	[110]
	SNALP	< 190	≈ 0	CTX	[111]
	PEG-lipid	60.97 ± 7.95		FAS	[76b]
	PEG-DSPE	90 ≈ 100		DCDX & c(RGDyK)	[112]
	T7&SHp-P-LPs/ZL006	96.24 ± 1.13	3.237 ± 0.206	T7 & SHp	[38]
	NFL-LNC	66 ± 4	6 ± 1.5	NFL	[113]
	DPM	119.7 ± 2.5	−54.3 ± 2.1	mApoE	[61b]

Table 1. Continue.

Type	Materials	Size [nm]	Charge [mv]	Ligand	Ref.
	PEG-DSPE	102 ≈ 118		RGD & pHA	[68]
	MF-PEG	212 ± 29			[40]
	PEG-DSPE	180 ± 12.5		Tf & F	[39]
	PEG-DSPE	≈100	−4.95 ± 0.59	R8 & c(RGDfK)	[61c]
	DQA-PEG_{2000}-DSPE-MAN-$TPGS_{1000}$	80 ≈ 90		MAN & DQA	[114]
	PEG-DSPE	186 ≈ 200	≈12	Tf & PR	[65b]
Inorganic-based	PHEMA-RA-PCB-CPP /SPIONS	≈ 100	2.6 @ pH = 7.4 15.4 @ pH = 3.5	Retinoic acid	[50]
	MNPs	212 ± 2.9	24 ± 1.9	GPNMB	[115]
	MNP-MSN-PLGA	≈150	−18.1 ± 0.5	Tf	[65a]
	WGA-HRP-Au	37.8	−28 ≈ −36	WGA	[116]
	CLIO	32	6.62		[117]
	PBCA-USPIO	252 ± 66	18.9 ± 2.5		[118]
	CUR-PEG-PLA-PVP-MNPs	< 100	−23 ≈ 0		[119]
	SiO_2	15 & 50	−11 ≈ −15		[120]
	Fe_3O_4@C	Sphere @ 172 ± 19 Spindle @ *L*: 250 ± 27 W: 84 ± 2 Biconcave @ *L*: 170 ± 12 W: 75 ± 17 Nanotube @ *L*: 322 ± 70 W: 150 ± 11 T: 50 ± 11	Sphere @ ≈ −30 Spindle @ ≈ −30 Biconcave @ ≈ −22 Nanotube @ ≈ −20		[121]
	CMX-MNP	CMX @ 172 ± 30	CMX @ −33.9 ± 0.8		[122]
	PEG-MNP	PEG @ 150 ± 33	PEG @ −39.6 ± 0.7		
	PEG-Au	20 ≈ 85	−5 ≈ −15	Tf	[47]
	DAK-PEG-Au	80	−5 ≈ −12	Tf	[48]
	Ag	49.7 ± 10.5	−27.8 ± 0.1		[53c]
	Au	5 ≈ 13.22	33.2 ± 0.43		[123]
	$CoFe_2O_4$@$BaTiO_3$	30			[52]
	Cy5.5-HFn	12 ≈ 15			[124]
	M-HFn	5.2 ± 1			
	Fe(0)@MCM-41	*L*: 250, W:100 ≈ 150, Pore *D*: 3.3			[53a]
	SiMNC	100 ≈ 155			[125]
	RVG-PEG-AuNRS@SiO_2	*L*: 117.7 ± 7.3 *D*: 50.3 ± 3.1	14.2 ± 2.5	RVG 29	[51]
	AuNC	70 ≈ 100	≈ −15	IgG	[126]

reticuloendothelial system uptake, slowed down the clearance of the nanomedicines, and were able to cross the BBB, thus improving the circulation time and allowing for more efficient penetration and accumulation in the brain. cis-Diamminedichloroplatinum (CDDP)-loaded PEG-coated NPs demonstrated deeper penetration in the brain tumor tissue, resulting in a much higher median survival rate compared to un-PEGylated NPs.[19]

Amphiphilic block copolymers can self-assemble into a range of micelle architectures which usually consist of a hydrophobic core and a hydrophilic corona extending into the aqueous environment. Because of their small size and unique narrow size distribution, interest in micelle nanocarriers is rising in the field of drug delivery.[15] These nanocarriers, both polymeric and phospholipid, can overcome the challenges presented by NPs, such as toxicity and rapid clearance from the body through the reticuloendothelial system.[20] These micelle nanocarriers can be further modified to allow greater drug encapsulation and penetration.[21] Studies have shown that the micelle delivery system has successfully crossed the BBB and penetrated the brain.[22] Examples of block copolymeric micelle nanocarriers include PEG-PLGA and PEG-PLA based NPs which demonstrate increased circulation lifetime and improved drug delivery across the BBB via conjugation of a function group, such as a protein or a targeting peptide.[23] For example, PEG-PLA NPs loaded with paclitaxel (PTX) and conjugated with tLyp-1

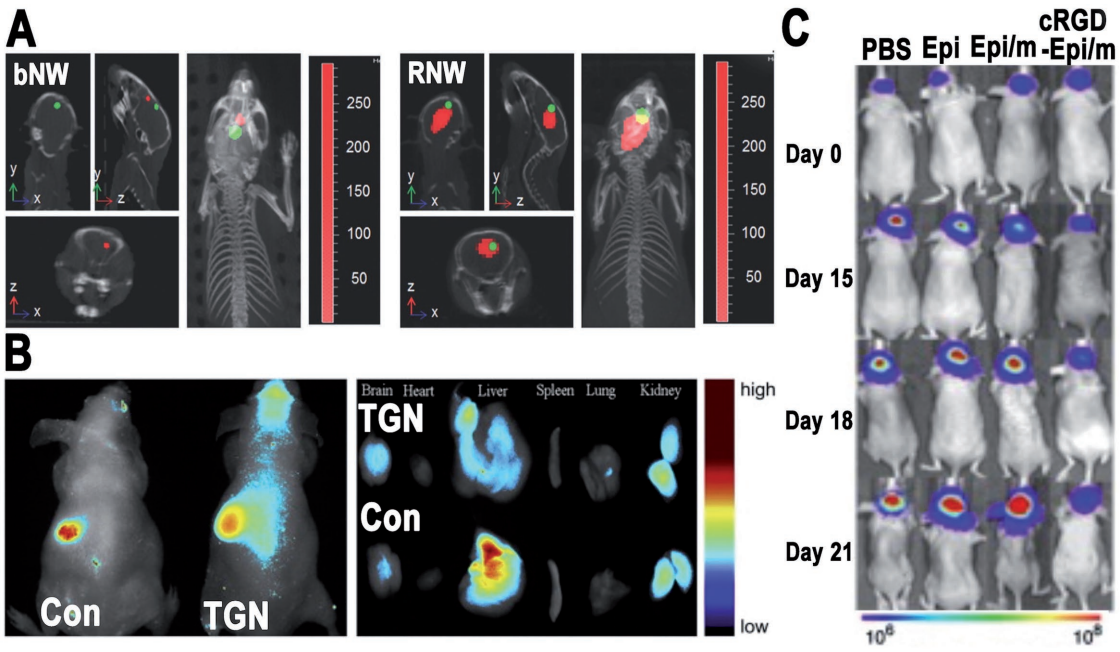

Figure 2. Bioimaging of micelles uptake in the mice brain A) In vivo bioimaging of bNW and RNW to the sites of the brain tumor 4 hour after injection.[25] B) The images of nude mice were treated with MPEG-PDMAEMA/DNA and TGN-PEG-PDMAEMA/DNA polyplexes.[27] C) Bioimaging of mice injected with PBS, Epi, Epi/m and cRGD-Epi/m at days 15, 18, and 21.[26] Reproduced with permission.[25] Copyright 2016, Wiley Publishing Group. Reproduced with permission.[26,27] Copyright 2013 and 2017, Elsevier.

peptide, the ligand with affinity to an overexpressed protein on glioma cells, significantly enhanced cellular uptake, increased the accumulation and penetration of PTX in the target cells, and inhibited the progression of the tumor.[24]

Recently, Zeng et al. demonstrated that nanoscaled wormlike micelles which is composed of mPEG-b-PDPA copolymer and combined with RGD peptide targeted cytotoxic emtansine conjugates are able to penetrate deep into the brain tumor and inhibit its progression. These micelles possess unique pH responsive properties and can be dissociated at intracellular acidic environments to release the therapeutic agent.[25] One research team studied a similar targeting of malignant cells by conjugating cRGD on PEG based micelles. In this study, the team developed PEG-cRGD micelles to enhance the penetration of the blood brain tumor barrier (BBTB). The results indicated that the cRGD-installed micelles possess the suppression property of an orthotopic glioblastoma multiform model and that they have targeting and penetration characteristics.[26] Moreover, PEGylated poly(2-(dimethylamino) ethyl methacrylate) (PEG-PDMAEMA) based micelles conjugated with the TGN, a 12-amino acid peptide, resulted in brain targeting properties similar to PEG-cRGD micelles. Additional micelle experimental results are presented in **Figure 2**. Despite many promising advantages, further research is needed to investigate micelles' biological stability, rate of drug dissociation, and drug retention time.[27]

2.1.2. Dendrimers

Dendrimers are stretched polymers and reactive 3D macromolecules, with regularly symmetric structure around the center. Different from regular polymers, dendrimers have more accurately controlled functional groups that can be modified with a desired moiety.[28] Covalent and noncovalent interactions are the major paths of interaction between dendrimers and drugs. The covalent reaction between stable bonds or cleavable bonds occurs when the materials reach the target. On the other hand, the noncovalent interaction is either drug encapsulation inside the dendrimers that enhances the drug solubility in aqueous solution, or electrostatic interactions between the drug and the surface.[29] A research team developed a carbosilane dendrimer loaded with fluorescein isothiocyanate (FITC) to deliver the siRNA to HIV-infected human primary astrocytes. The modified dendrimer reached the infection area successfully and achieved gene silencing in the mice model.[30] Recently, Zhang et al. engineered different sizes of poly(amidoamine) (PAMAM) based dendrimers to investigate the effect of size on the uptake rate into the brain. Interestingly, the ≈6.7 nm PAMAM based dendrimer appeared to not only extend blood circulation times but also enhance accumulation of dendrimers in the injured brain more than the ≈4.3 nm dendrimer. Whereas this result offers insights into dendrimers as carriers in BBB delivery,[31] due to the low targeting efficacy of dendrimers as carriers in BBB delivery, few research teams are conjugating targeting ligands on the surfaces of dendrimers to increase BBB targeting and penetrating. One research group used poly(propylene imine) (DAB) based dendrimer conjugated with transferrin (Tf) to increase gene expression in the brain. They noticed that with the conjugated dendrimer, the gene expression in the brain was at least threefold higher than with the nontargeted dendriplex and naked DNA.[32] The same group also found that conjugating lactoferrin on the DAB based dendrimer presented

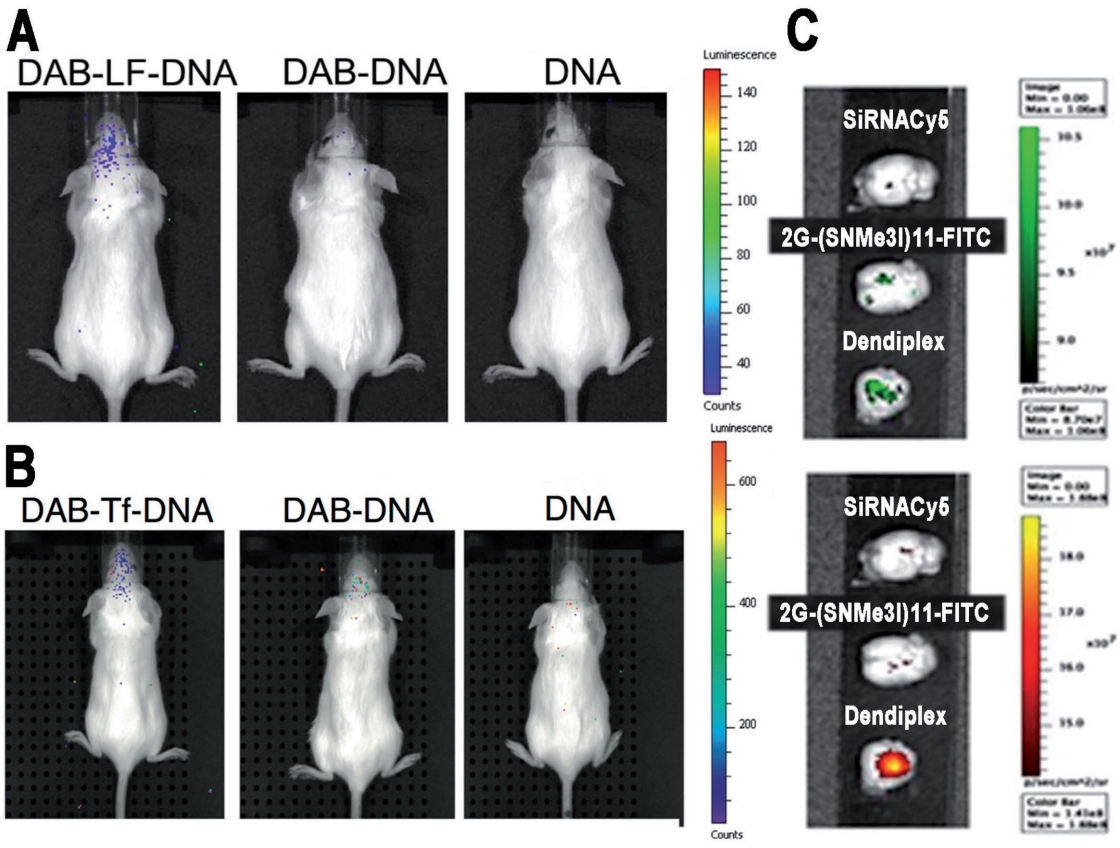

Figure 3. The bioimaging of dendrimers uptake in the mice brain A) Bioluminescence imaging of gene expression of DAB-LF-DNA, DAB-DNA and DNA.[33] B) Bioluminescence imaging of gene expression of DAB-Tf-DNA, DAB-DNA, and DNA (50 µg DNA administered).[32] C) The bioimaging of SiRNACy5, 2G-(SNMe3I)11-FITC/siRNA/dendriplex expression from brain of inoculated mice.[30] Reproduced with permission.[30,32,33] Copyright 2014 and 2015, Elsevier.

superior gene expression in mice brain—the modified dendriplex had about 6.4-fold higher expression than the nontargeted dendriplex and naked DNA.[33] Additional dendrimer experimental results are shown in **Figure 3**. However, unlike the auspicious properties of polymers such as PLGA and PLA, the long-term safety issues and unpredictable drug release kinetics associated with dendrimers limit their wide application in BBB delivery. Further chemical optimization in the parent molecules is needed to improve their performance in brain drug delivery applications.

Polymer-drug conjugates are another category of polymeric nanocarriers that have been widely investigated over the past two decades, with an increasing number of polymer conjugates have progressed to clinical trials. For example, ProLindac (HPMA copolymer–diaminocyclohexane palatinate) is currently under clinical phase II development for treating recurrent ovarian cancer, and FCE28069 (HMPA copolymer–doxorubicin (DOX)-galactosamine) is in phase II for hepatocellular carcinoma.[34] Although there are no polymer-based therapeutics in clinical trials for CNS diseases yet, their ability to precisely target cells and control drug release makes polymer–drug conjugates viable therapeutic options. Continued research needs to be performed to yield success in the development of novel polymeric nanocarriers capable of controlled and targeted drug delivery to the brain across the BBB.

2.2. Lipid-Based NPs

Liposomes are spherical bilayered phospholipid vesicles enclosing an aqueous inner core. They can be made from cholesterol, fatty acids, or phospholipids. Because of their biocompatible and biodegradable properties, liposomes have the affinity to target BBB and increase circulation time.[35] Due to their hydrophilic and hydrophobic components, liposomes can encapsulate water-soluble and lipophilic drugs, thus increasing their bioavailability in the body. Their sizes, charges, and compositions can be easily adjusted to allow for effective transportation of bioactive molecules, such as nucleic acids, enzymes, and proteins. Conjugating ligands and monoclonal antibodies corresponding to the receptors on the BBB onto liposomes have been found to facilitate the transport of drugs across the BBB. In addition, liposomes can trap both hydrophobic and hydrophilic groups, which restricts the decay of the materials and allows for a controlled and precise release at the targets.[36] Due to these unique and advantageous properties, liposomes have been widely used as nanocarriers to cross the BBB for the treatment of various brain diseases. One study used *p*-aminophenyl-α-D-mannopyranoside (MAN) based liposome (MAN-LIP) to determine the distribution of glucose and liposome transporters on the cells. They found that the MAN-LIP had high accumulation in mice brain. In addition,

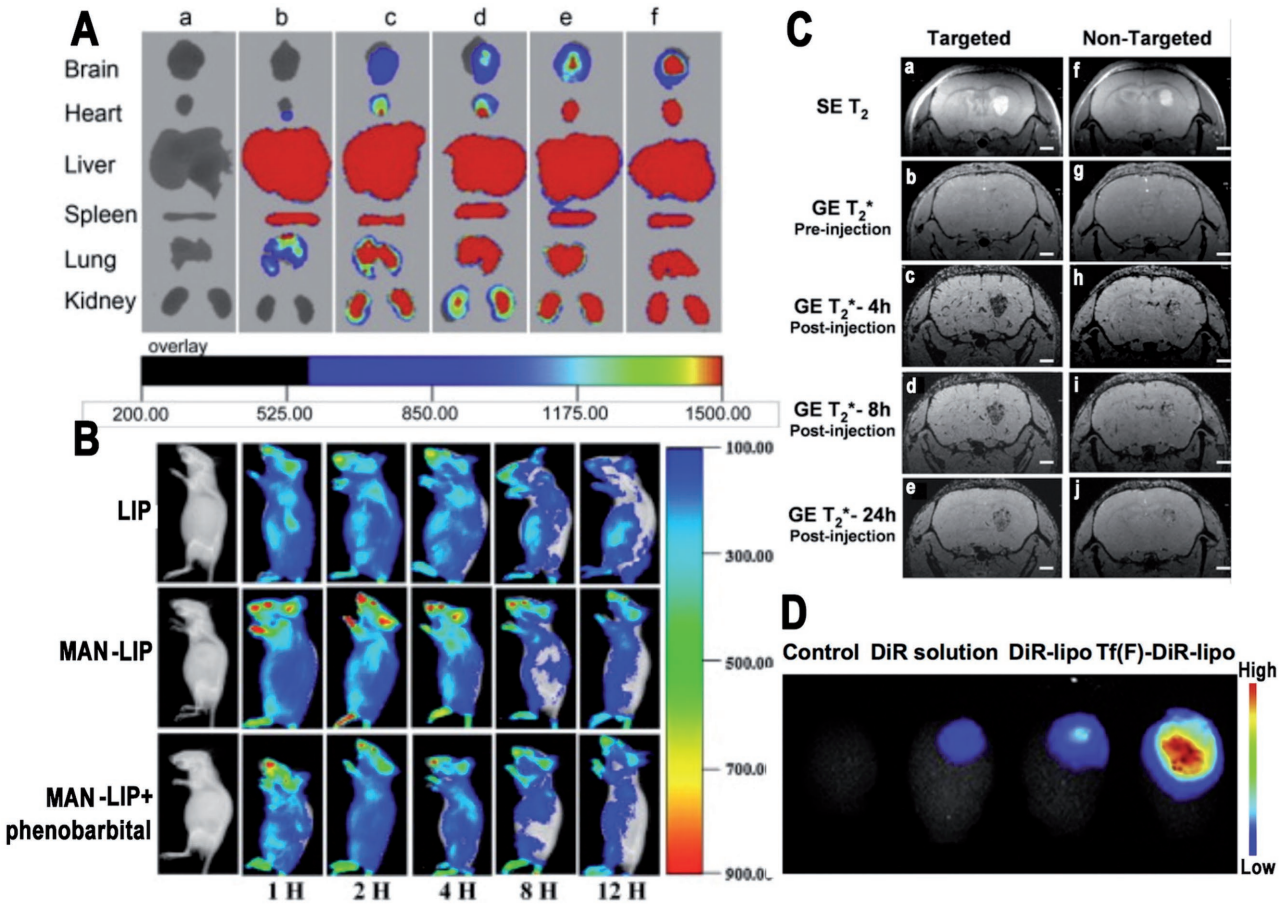

Figure 4. The uptake evaluation of liposome based nanocarriers in mice model A) Bioimaging of targeting liposomes in mice (a) saline, (b) free DiR and (c) DiR, (d) MAN-DiR, (e) DQA-DiR, (f) functional targeting DiR liposome.[114] B) Bioimaging of mice after intravenous injection of varied composition.[37] C) MRI images of brain with targeting liposome (a–e) or without liposome (f–j) in different times.[39] D) In vivo imaging in distribution of Tf (F)-dox-liposome of mice at 24 h.[39] Reproduced with permission.[37,39,114] Copyright 2013 and 2014, Elsevier. Reproduced with permission.[40] Copyright 2015, Wiley Publishing Group.

they also demonstrated that when GLUT1 and GLUT3 were overexpressed, the MAN-based liposome presented better transendothelial ability in crossing LV-GLUT1/GLUT3/bEND.3 cell monolayers, indicating that it is a potential drug delivery carrier to the brain.[37] As a result of the permeability and targeting properties of the liposome based carriers, the dual targeted liposome was regarded as a more attractive nanocarrier in drug delivery field. Zhao et al. developed a liposome based dual targeted nanocarrier conjugated with T7 peptide (T7) and stroke homing peptide (SHp) to treat brain ischemic stroke.[38] Moreover, one research team demonstrated that the duel targeted liposome was able to penetrate the BBB and subsequently target glioma cells. The group reported the use of the DOX based liposome with Tf and folate ligand. The results showed that the dual targeting liposome increased the therapeutic efficacy of glioma in the brain and presented less toxicity than the control group (DOX solution only).[39] Additional liposome experimental results can be found in **Figure 4**. Furthermore, a magnetic fluid liposome based nanocarrier, which provides noninvasive traceability, has been engineered. This iron oxide loading liposome possesses the ability to precisely target the glioblastoma, and provides great selectivity that increases the enhanced permeability and retention (EPR) effect while sparing the healthy brain.[40]

2.3. Inorganic-Based NPs

Inorganic NPs, including gold (Au), iron oxide, silica, and silver, among others, are widely used for applications in brain drug delivery as they possess unique characteristics compared to their polymeric and lipid-based counterparts.[41] Inorganic NPs can be easily modified to facilitate conjugation of ligands or polymers, thereby improving their biological performance.[42] Additionally, it is possible to precisely tune parameters such as size, shape, or porosity of inorganic NPs for therapeutic and diagnostic applications in brain diseases.[43] Furthermore, particular external stimuli such as near-infrared (NIR) radiation and the application of a magnetic field can facilitate on-demand drug release across BBB and enhance imaging.[44] For example, an AuNP with surface modifications provides an interesting platform for nanocarriers in the drug delivery system. Mirkin's group developed a DNA modified AuNP based diagnostic probe for AD disease, which offered reliable detection

capabilities of the amyloid-β-derived diffusible ligands.[45] This group also developed a surface engineered theranostic AuNP that demonstrated BBB and solid tumor penetration properties both in vitro and in vivo. This unique platform exhibited high selectivity, no toxicity, and stunning targeting characteristics, making it as superior nanocarrier for brain drug delivery.[46] Additionally, AuNPs functionalized with Tf showed remarkable capability of deeply penetrating the brain parenchyma of mice through a receptor transcytosis pathway after systemic administration.[47] AuNPs coated with Tf with an acid cleavable linkage shows larger amounts of particle accumulation in mice brain than that of noncleavable TfNPs due to the cleavable process, which allowed a greater release into the brain.[48]

Superparamagnetic iron oxide NPs (SPOINS), or iron oxide NPs (IONPS), in combination with magnetic resonance imaging(MRI) has been rising in brain drug delivery filed recently.[49] Zhang et al. synthesized a traceable SPOINS system by using a poly(carboxybetaine) polymer-based NP and conjugated cell-penetrating peptide (CPP) as the targeting ligand. Due to enhanced proton relaxation in the brain tissue, enhanced MRI contrast was observed.[50] Another study demonstrated that the application of an external magnetic field mediated the ability of magnetic NPs (MNP) to permeate the BBB and accumulate in the brain, with no observable toxicity. It has been suggested that endothelial cell membrane-mediated translocation of MNPs may be a possible mechanism for the BBB crossing, while allowing the BBB to remain intact. Magnetic disruption of the BBB provides a harmless method of drug delivery via MNPs.[51] It has also been reported that MNPs possess the capability to remotely control drug delivery.[52]

Many studies have been shifting their focus toward silica-based, carbon-based or sliver-based NP systems to deliver therapeutic agents into the brain when restricted by the BBB.[53] Additional inorganic NP experimental results are shown in **Figure 5**. Despite the fact that inorganic NPs possess many unique

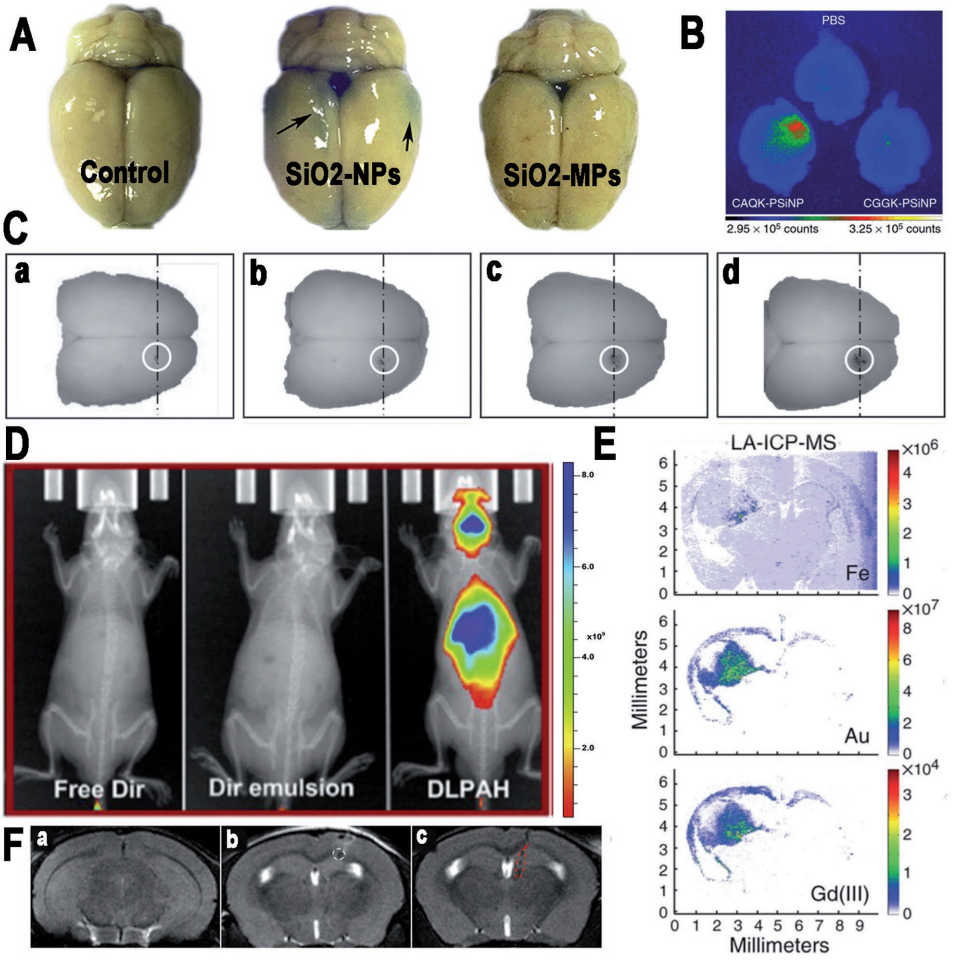

Figure 5. The in vivo imaging comparison of NPs in mice model A) Images of the brain from left to right: control, SiO_2-NPs, and SiO_2-MPs.[132] B) In vivo fluorescent imaging of PBI mice injected with vehicle alone (PBS) or PSiNPs conjugated with CAQK or CGGK.[133] C) The in vivo images of the brain at 3 h post PTI (a) without NPs administration (b) with 60 nm NPs (c) 30 nm NPs, and (d) 10 nm NPs.[57] D) Bioluminescent images of mice without Dir, with Dir emulsion or DLPAH nanoclusters via tail vein at 12 min after administration.[134] E) Laser ablation images of Au, Fe, and Gd (III) in mice brain.[46] F) In vivo T2 MRI images of brains, before (a) and after administration of ABC/SPIONs/siSOX9 NPs for 1 d (b) and 35 d (c).[50] Reproduced with permission.[132,134] Copyright 2017, Elsevier. Reproduced with permission.[50,57] Copyright 2016, Wiley Publishing Group. Reproduced with permission.[46] Copyright 2013, AAAS Publishing Group. Reproduced with permission.[133] Copyright 2016, Nature Publishing Group.

advantages, they have yet to be approved for drug delivery. Few have entered clinical trials as toxicity and in vivo clearance remain limiting factors in the application of inorganic NPs for the treatment of brain diseases. Use of different materials will further affect the result of drug delivery system because of the properties of individual platform; for example, polymeric and lipid-based NPs have the advantage of biodegradability, biocompatibility, controllable size, surface manipulation, and high drug loading rate; however, the low circulation time, large NPs size, poor targeting efficacy, and difficulty in uniform bench production are the major disadvantages of these NPs. On the other hand, the inorganic NPs possess long EPR effect, enhanced bactericidal activity, unique size, low cost, easily modification characteristics; nonetheless, the major drawbacks are low efficacy of targeting, nondegradability and potential toxicity which still cannot be solved in the current clinical stage.

3. Physicochemical Properties and Delivery Methods of Nanocarriers Affect their Transport across the BBB

There are many variables that affect the delivery and efficacy of drug loaded NP systems into the brain. Understanding the composition of the nanocarriers and their affinities and interactions with proteins/receptors on the BBB will allow nanoformulations to cross the BBB successfully. In general, the size, charge, shape, surface ligands, and method of delivery can be manipulated to enhance brain permeability and bioavailability of the therapeutic drug. We will discuss several variables, that when optimized, can enhance the uptake of therapeutics across the BBB, thus allowing for greater efficacy than traditional therapy.

3.1. Size

Size is a significant design factor that directly affects NP uptake and permeability into the brain and can be tuned by carefully controlling the nanomaterial preparation process. Different sizes can trigger various biological phenomena such as circulation half-times, extravasation through leaky vasculature, and macrophage uptake.[54] In principle, NP size ≤200 nm is a better selection to cross the BBB. For example, 100 nm PLGA-PEG NPs exhibit deeper brain penetration and longer circulating time than that of the 200 and 800 nm NPs.[55] Similarly, it has been demonstrated that 60 nm PS-PEG particles combined with ultrasound techniques to disturb BBB, can be more diffusive in the normal rat brain than the 110 nm NPs.[56] Furthermore, one study used 10, 30, and 60 nm biocompatible NIR NP; the 10 nm NPs showed poor selectivity, the 30 nm NPs were the most sensitive and selective for BBB damage evaluation, and the 60 nm NPs barely crossed the BBB.[57] In this particular BBB damage imaging/evaluation case, both the 10 and 30 nm NPs can cross the BBB. However, the 10 nm NPs can penetrate and leak from nonischemic region of the brain and therefore is not very suitable for BBB damage evaluation. Additionally, a 60 nm particle cannot cross the damaged BBB due to the bigger size. As such, a 30 nm particle showed superior capability for BBB damage evaluation. Although smaller sized NPs are transported through the BBB more easily, they lead to limited encapsulation efficiency, rapid drug release, and restricted surface energy in the endocytosis process. Moreover, very small NPs (≤5 nm) are vulnerable to renal excretion, and can be easily secreted from target tissues/organs even they after escape from renal excretion particularly in tumor tissues because of the EPR effect.[58] For the development of brain targeting nanocarriers, a size of ≈20 nm is thought to be sufficiently small to cross BBB and large enough to escape renal excretion, albeit particle shape and surface charge further affect the uptake rate of NPs.

3.2. Charge

The charge of a NP can result in diverse circulation lifetimes and can selectively enhance accumulation at a specific site of interest. Generally, positively charged NPs are known to be more easily internalized into the cell than neutral and negatively charged NPs because of negatively charged nature of cellular membrane. Nevertheless, NPs with neutral and negative charges have been demonstrated to reduce the adsorption of serum proteins, resulting in longer circulation half-times.[59] Furthermore, neutral NPs and low concentrations of anionic NPs were found to have no effect on BBB integrity, whereas, the BBB was proven to be disrupted when using cationic NPs and high concentrations of anionic NPs.[60] Hence, abundant research in surface charge of nanocarriers has been investigated in the past decade.[61] Zhang et al. conjugated a negatively charged (−29.6 ± 3.6 mv) peptide (peptide-22) to PEG-PLA based NPs, which was proven to be beneficial in enhancing both BBB penetration and intracellular delivery to glioma cells.[62] It has also been reported that a near neutral surface of a PAA-PEG NP enabled the drug payload of CDDP as well as the drug carrier to rapidly diffuse within the brain tumor.[18] It is important to note that the fate of the NP is not always consistent with the original surface charge. Protein absorption onto the NP surface can form protein corona and can lead to the shift of zeta potential to slightly negative surface charge regardless of its original positive surface charge. In this regard, both in vitro and in vivo cellular uptake of nanocarriers by phagocyte or target cells should be tested before further investigation on formulation efficacy. The effects of surface charge on target cell uptake, particle biodistribution, and interaction with biological systems including BBB should be born in mind during the design of NP-based drug delivery systems.

3.3. Ligand

As a result of their inadequate targeting abilities, many nanocarriers developed to encapsulate drugs fail to cross the BBB and reach the disease tissues. To facilitate BBB penetration, a number of ligands have been successfully conjugated or absorbed to NPs. Major targeting moieties used to modify the nanocarriers' surface include antibodies, engineered antibody fragments, peptides, aptamers, sugars, and small molecules.[63] The main targeting mechanism is the recognition and selective binding of the ligand on its target substrates, particularly

on surface molecules or receptors overexpressed in diseased tissues, organs, and cells. This strategy features as active targeting, also called ligand-medicated targeting. The ligand density can be fine-tuned in the particle synthesis/formulation process to optimize the avidity, overcome delivery barrier, and achieve spatial localization. For example, Tf receptor (TfR) is often overexpressed on the BBB and brain tumor cells.[64] Due to this occurrence, many studies have shown that the Tf targeting ligand on the NPs can not only engage TfR at the BBB, but can also increase the BBB penetration and accumulation of encapsulated drug, thereby enhancing the therapeutic performance towards tumor cells.[47,65] More importantly, Tf has been already used in clinical trials.[66] Among a growing list of candidates, Qiang et al. demonstrated that TGN can be modified onto the surface of PEG-PDMAEMA micelles. TGN has great potential in facilitating BBB targeting, leading to a much higher accumulation of NPs in the brain.[27] In an effort to enhance the efficacy of penetration and targeting of brain diseases, this team developed a dual-functional PEG-PLA NP system modified with both TGN and QSH targeting ligands in the treatment of AD. The TGN peptide was first employed as a targeting ligand to successfully pass though the BBB and the QSH peptide allowed the nanocarrier to reach the AD disease cells. The modified NPs achieved 3.6 times more accumulation in the brain than unmodified NPs.[23b,67] Building upon the same idea, one research group created a liposome based carrier modified with RGD and pHA ligands, which allowed the liposome to successfully cross the BBB and penetrate the BBTB. In vivo fluorescence imaging indicated that the liposome modified with two ligands had better distribution than ligands with single or no modifications.[68] Additional types of ligands used for active targeting include CPP, folates, des-octanoyl, angiopep-2, polysorbate 80 (PS-80), lactoferrin (Lf), immunoglobulin G (IgG) and insulin, among many others.[16b,53b,69] Despite promising findings in preclinical studies, the superior therapeutic efficacy of active targeting nanoformulations has not yet been convincingly demonstrated in humans. The interaction of NPs and physiological proteins in serum as well as factors that interrupt the orientation of the targeting ligands highlight the need for further investigation of BBB targeted nanomedicines.

3.4. Shape

Interestingly, the shape of NPs, which can vary from spherical to rod-like, also impacts BBB passage, systemic circulation, cellular uptake, and hemorheological dynamics (**Figure 6**).[70] Various shapes of NPs can be synthesized from both "top down" and "bottom up" approaches.[71] Most of the research studies have been conducted with spherical NPs since they are relatively easy to manufacture. However, the curvature of spherical NPs allows limited binding sites with membrane receptors on the surface of an endothelial cell and can cause undesirable side effects in circulation and accumulation.[72] As such, a large number of studies focused on the improvement of aspect ratios and reduction of regional curvature. For instance, one research team showed that filomicelles stayed in circulation up to 7 d, nearly tenfold longer than their spherical counterparts (2–3 d).[73] It has been demonstrated that shape also affects NP biodistribution. The majority of PTX loaded filomicelles were found to remain in circulation longer than spherical micelles and doubled the maximum tolerated dose.[74] Kolhar et al. reported that polystyrene nanorods coated antibodies lead to higher accumulation in brain endothelium compared to spherical NPs.[75] Au nanorods coated with a RVG 29 ligand of rabies virus enabled them to overcome the BBB and enter the CNS. Their rod shape specifically enhanced their interaction with the nicotinic acetylcholine receptor expressed on neuronal cells, thus allowing them to be internalized more rapidly than the spherical counterparts.[51] It is evident that altering the shape of nanocarriers can influence their uptake into the brain, whereby increasing the efficacy and bioavailability of therapeutic agents. We speculate that variant shaped of NPs such as disk-like and ring-like, provide better targeting and penetrating properties than widely used spherical NPs and should be investigated further as potential carriers in drug delivery.

3.5. Delivery Methods

As a result of the selective nature of the BBB, many nanoformulation administration methods have been explored to deliver therapeutic drugs. Regardless of different administration routes, the objective of studies is to evaluate the potential of nanomaterials to deliver therapeutic agents across the BBB and improve clinical outcomes. The most common mode of nanomedicine administration method is intravenous injection. Unfortunately, the injectable method is faced with the challenge of rapid clearance from the body through the reticuloendothelial system, leading to frequent injections and limited therapeutic effect. Although delivery to the blood circulation has the benefit of providing drug access to any vascularized tissues including brain, this pervasive access also results in unintended tissue/organ drug accumulation such as in the liver and spleen. For many diseases, alternative routes of administration have found to be more effective than systemic delivery. In fact, some nonconventional nanomedicine administration routes have already demonstrated preclinical benefits, including ultrasound assisted nanomedicine delivery, intranasal administration, and oral delivery.

3.5.1. Ultrasound Assisted Delivery

Most studies focus on using nanoscale drug carriers, such as NPs, liposomes, and micelles[17,38] or conjugating drugs with targeting ligands such as peptides, folates, glycans, and antibodies as a means of disrupting the BBB to enhance the efficiency of therapeutic agents in tumor cells.[69a,76] Although nanocarriers can enhance drug delivery, the BBB still imposes extreme restrictions on the distribution of therapeutic agents in reaching their target. Meanwhile, delivering drugs surgically brings limited therapeutic effects.[77] The impairment of the tumor is often heterogeneous, which also causes an undesirable pressure gradient for further drug penetration.[78] Additionally, traditional therapies bring several disadvantages, such as postoperative infections, neurotoxicity, and complication during procedures.[79] Alternatively, a more efficient technology,

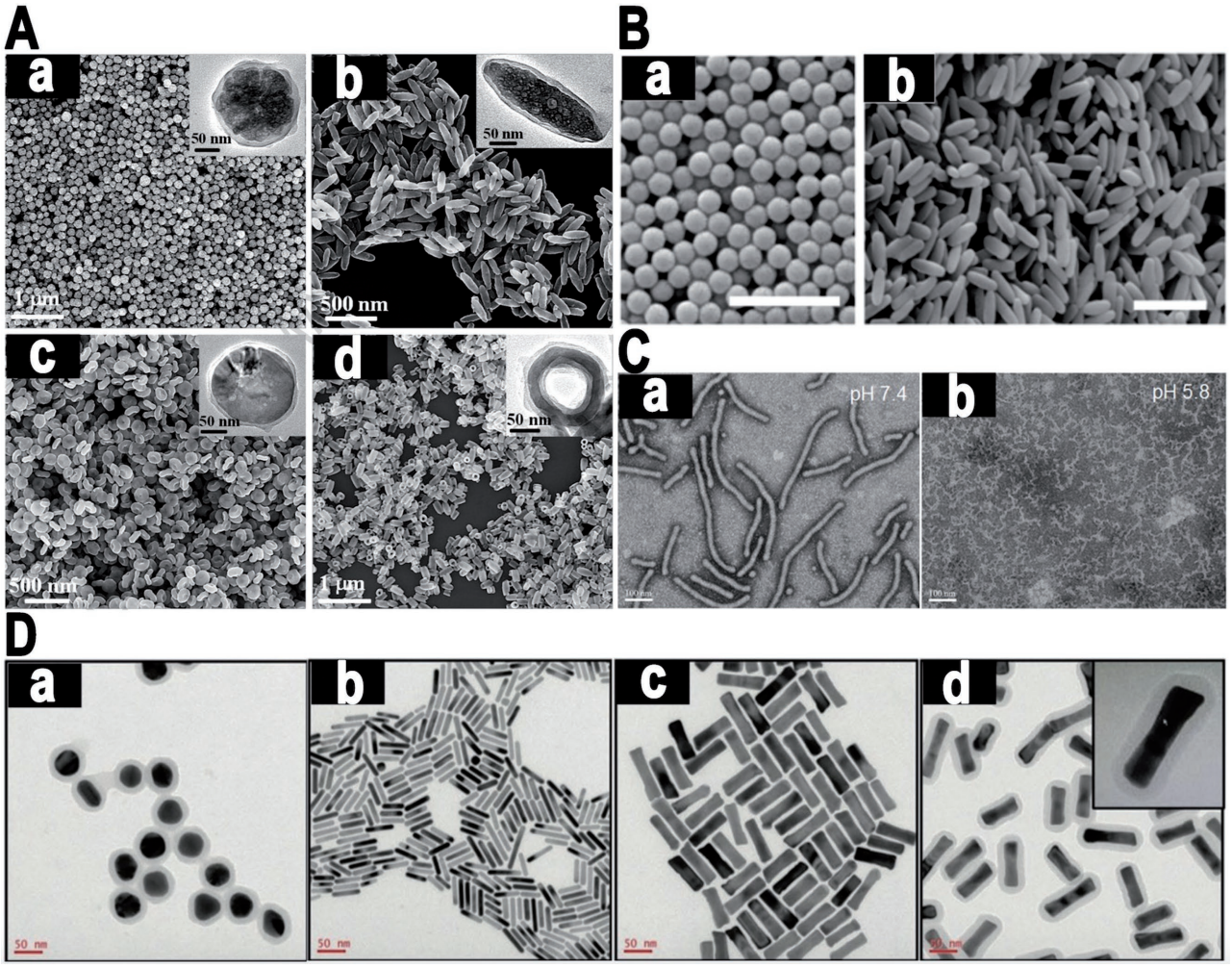

Figure 6. Characterization of nanocarriers in several shapes A) FESEM images of different shapes of Fe_3O_4: (a) sphere, (b) spindle, (c) biconcave, (d) nanotube.[121] B) SEM images of polystyrene spheres (a) and elongated particles stretched from the 200 nm spheres (b). Scale bar, 1 μm.[75] C) TEM images of nanocarrier at pH 7.4 (a) and 5.8 (b), scale bar = 100 nm.[25] D) TEM images of morphologies in AuNRs (a) and AuNRs (b) (c) (d) at different steps.[51] Reproduced with permission.[121] Copyright 2015, Elsevier. Reproduced with permission.[75] Copyright 2013, PNAS. Reproduced with permission.[25,51] Copyright 2016 and 2017, Wiley Publishing Group.

an ultrasound-based method, has been exploited to open the BBB transiently, safely, and reversibly in a targeted manner.[80]

The application of ultrasound-based techniques to penetrate cellular membranes and vascular endothelium is referred to as cellular sonication, which profits considerably from the combination of micro or nanoscale bubbles to mediate a substantial brain delivery of nanoscale agents. The mechanism regulating the interactions between the bubbles and their surrounding endothelial cells is thought to result from radiation force and shear stress on the vascular walls when the microbubbles oscillate in feedback to the acoustic stimulus after an ultrasound exposure, leading to a transient, reversible, and noninvasive opening of the BBB through physiological and cellular processes[81] and enabling nanoscales access to the CNS. Mulik et al. described that targeted delivery of docosahexaenoic acid, a therapeutic agent, is likely to conjugate low-density lipoprotein NPs across the BBB when accompanied with pulsed focused ultrasound exposure. A near IR fluorescent dye (i.e., DiR) was used as a tracer to visualize the accumulation of agents, which was over 60-fold greater compared to the counterparts administered without focused ultrasound exposure. Meanwhile, there has been no evidence of harmful sides effects such as cytotoxic and acute neuronal damage as a result of focused ultrasound.[82] Yao et al. facilitated drug delivery in the brain via PEG-PLA NPs and ultrasound-induced stable cavitation of microbubbles. To treat AD, they conjugated a beta-specific antibody 6E10 on PEG-PLA, and used fluorescent probes including coumarin 6 and DiR to evaluate the accumulation of nanoparticulate drug delivery. After the ultrasound exposure, the PEG-PLA NPs penetrated across the blood vessel wall and distributed in the parenchyma up to 2.5-fold more than the counterparts without ultrasound treatment.[83] Research showed that with the aid of ultrasound techniques and a novel gas-cored nanobubble, siRNA complexed in PEG-b-poly(L-Lysine) (mPEG-

Table 2. Delivery of nanomaterials across the BBB using ultrasound.

Type	Materials	Size [nm]	Charge [mv]	Ref.
NPs	PEG-PLA	105.4 ± 33.0 @ Coumarin 6	−27.50 ± 1.15 @ Courmarin 6	[83]
		106.7 ± 33.9 @ Dir, 129.0 ± 41.7l @ Fe3O4	−28.01 ± 0.7 @ DiR	
NPs	PS-PEG	40 ≈ 200	−0.7 ≈ −40	[56]
NPs	PBCA	177	−12	[127]
NPs	DNA-BPN	106–130	−2 ≈ 2	[128]
NPs	NMGO-mPEG-EPI	120 ≈ 150		[80]
NPs	PAA-PEG	45.3 ± 2.5 ≈ 65.0 ± 5.1	−3.27 ± 0.48 ≈ −35.2 ± 0.54	[79]
Nanodroplet	DSPC-PEG	200 ≈ 300		[129]
Liposome	Lipo-DOX	≈ 100		[130]
MNBs	PS-OTES/TEOS/ APTES-SPIO	200 ≈ 2000	−8 ≈ −28	[131]

b-PLLys), was increased and transferred into glioma cells by tenfold.[84] More ultrasound experimental results can be found in **Table 2**. Delivering nanocarriers by means of ultrasound disruption in combination with nano- and microbubbles is a promising strategy of BBB modulation that is continuing to be developed and studied further.

3.5.2. Intranasal Administration

Over the last several decades, the intranasal administration has been progressively utilized in trials to deliver therapeutic nanoagents and to treat specific brain diseases, owing to the unique olfactory and trigeminal pathways.[85] The nasal route can not only directly deliver the drug to the brain via bypassing the BBB, but can also escape hepatic first-pass and gastrointestinal elimination. Meanwhile, intranasal delivery provides a noninvasive way to delivery therapeutic agents to target brain cells.[86] Nevertheless, intranasal administration is faced with constraints in reaching the olfactory region and limitations in enhancing the transport across the olfactory membrane.[87] One research found that PEG-PCL nanosized micelle modified with a CPP (PEG-PCL-Tat), administered intranasally, accelerated the transport of the therapeutic agent along the olfactory and trigeminal nerve pathway and led to an increased delivery of Alexa-dextran, a siRNA model, compared to that of intravenous administration.[88] Recently, another research demonstrated that Lf-conjugated PEG-PCL NP(Lf-NP) has great potential to serve as an intranasal drug delivery carrier especially for delivering peptides and proteins. This study also showed that the area under the plasma concentration-time curve in 0–8 h ($AUC_{0\text{-}8h}$) ratio of brain tissues to blood of coumarin-6 incorporated in Lf-NP was approximately twofold higher that of the unmodified NPs.[16b] Although targeting of nanomaterials via intranasal route by bypassing the BBB brings promising opportunities for brain diseases, the ability to remotely control release, monitor pharmaceutic long-term effect, and improve variability in the amount of drug absorbed still need to be investigated further.

3.5.3. Oral Delivery

Oral delivery provides enhanced patient compliance owing to its convenient administration. Nevertheless, oral delivery of therapeutic agents via nanocarriers not only needs to overcome the challenges described above, but must also survive the harsh enzymatic environment of gastrointestinal tract and efficiently cross the intestinal epithelial barrier to reach systemic circulation. Very few studies on oral administration have been reported due to poor drug absorption into systemic circulation and insignificant bioavailability of drug.[89] One research evaluated oral administration of poly(butylcyanoacrylate) (PBCA) NPs coated with PS-80 and PEG for brain delivery.[90] However, PBCA is thought to have toxicity problems as a result of the noxious mixture formed after its degradation by hydrolase enzymes.[91] Mittal et al. have shown that, while limited variability was a problem, orally administered PS-80 coated PLGA NPs that can deliver estradiol, which protects against stroke-induced brain damage, were as efficient as intramuscular administration in restraining and weakening the pathological process of AD.[92] Consequently, the objective of oral delivery remains arduous to achieve, and in the future, research should concentrate on controlling release, enhancing bioavailability, and improving variability in situ absorption.

4. Conclusion and Perspective

The NP-based drug delivery field has made considerable progress in recent years, including substantial achievements in the brain-targeted drug delivery area. However, while the arrival of nanotechnology presents many new opportunities, there still remains much to be learned in the emerging field of nanomedicine for brain delivery, including prominent uncertainties regarding optimal nanomedicine formulations. As a proof-of-concept, varieties of nanomedicine formulations and drug delivery approaches that have been navigated across BBB are limited only in vitro or in vivo animal models. While some nanomedicine formulations are already in clinical trials, and many others are in various phases of preclinical development, we have yet to develop a carrier that can effectively deliver a payload across the BBB specifically with clinically validated results for commercial use. It is worth noting that most NP-based formulations for brain drug delivery still accumulate significantly in other regions of the body, such as the liver, spleen, lungs, kidneys, among other organs/tissues, before being cleared out. Additionally, the uncertain potential health hazard of nanomaterials remains the most challenging hurdle for regulatory approval and commercialization of nanomedicine. The interactions between a therapeutic, the nanomaterial carrier, the immune system, and the biological barriers, are complex and their net effects on the spatial kinetics of the therapeutic are largely unknown. Besides the complications in

the experimental evaluation of brain targeting NP formulations, there exist multiple challenges in the scale up, regulation, and approval for clinical use. These various issues represent interesting and potentially fruitful research opportunities for further development in the next generation of brain drug delivery systems and their clinical evaluation.

Overall, in the field of brain diseases, the complexity of the disease might necessitate joint efforts of multidisciplinary teams. From a clinician/scientist perspective, drug delivery biological barriers and disease mechanism(s) must be thoroughly elucidated and understood. A fully developed understanding of the interactions between nanomaterials and biological systems will open the door to rational designs of nanomedicines, hence improving their biodistribution. In parallel, material scientists may develop advanced nanomaterials and robust methods for the design, synthesis, and characterization of NP-based systems to overcome the hurdles in BBB crossing. In general, an ideal nanocarrier/nanoformulation used for the brain drug delivery should have the following salient features: (i) biodegradable and biocompatible; (ii) capable of crossing the BBB and effective homing to the brain, with most of the therapeutic agent localized within the target site; (iii) avoid or protect drug from hydrolytic or enzymatic degradation; (iv) designed with optimal bio-physicochemical properties for superior drug loading, circulation half-life, and sustained drug release format with infrequent administration times; and (v) amenable to cost-effective scale up for commercialization. In our opinion, the particle size for effective therapeutics delivery to brain should be in the range between 10 and 150 nm. Too small NPs are vulnerable to renal excretion and clearance from target tissues.[93] Evidently, surface charge affects the fate of NPs administered in biological systems in terms of toxicity, circulation half-life, bio-distribution, cellular uptake, and interaction with delivery biological barrier. For instance, increased pulmonary toxicity and decreased circulation half-life usually has been observed for cationic NPs when compared with their anionic or neutral counterparts. It is critical to develop modalities to enhance the bioavailability of nanoformulations in target organ. In principle, surface ligands which bind to surface receptors abundant in brain endothelial cells can facilitate BBB penetration.[11] For example, the combination of a receptor-targeting agent (i.e., Tf) and CPP in a NP delivery vehicle can enhance the delivery of associated therapeutic cargo across the BBB and has shown improved translation of small molecules and genes into brain.[94]

In summary, the application of nanomaterials in the realm of therapeutics delivery across the BBB has demonstrated tremendous potential from the early diagnosis of the disease to the development of highly effective brain targeted therapeutics. Despite the significant challenges that exist, including scientific concerns and regulatory issues associated with the commercialization of nanomaterial-based medical products, the development of brain-targeting nanomedicine holds enormous promise for the future treatment of complex diseases. Critical assessment of clinical needs and improved understanding of disease biological mechanisms, coupled with rational design of brain-targeting NP- based drug delivery system will foster the development and translation of nanomedicine from bench-side to bedside.

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Conflict of Interest

The authors declare no conflict of interest.

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