NIH Public Access
Author Manuscript
Drug Discov Today. Author manuscript; available in PMC 2014 November 01.

Published in final edited form as:
Drug Discov Today. 2013 November ; 18(0): 1074–1080. doi:10.1016/j.drudis.2013.06.010.

Image-guided drug delivery to the brain using nanotechnology

Hong Ding[1], **Fang Wu**[2], and **Madhavan P. Nair**[1]

[1]Department of Immunology, College of Medicine, Florida International University, Miami, FL 33199, USA

[2]Department of Pharmaceutical Sciences, The State University of New York at Buffalo, Buffalo, NY 14260, USA

Abstract

Targeting across the blood--brain barrier (BBB) for treatment of central nervous system (CNS) diseases represents the most challenging aspect of, as well as one of the largest growing fields in, neuropharmaceutics. Combining nanotechnology with multiple imaging techniques has a unique role in the diagnosis and treatment (theranostics) of CNS disease. Such imaging techniques include anatomical imaging modalities, such as magnetic resonance imaging (MRI), ultrasound (US), X-ray computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT), electron microscopy, autoradiography and optical imaging as well as thermal images. In this review, we summarize and discuss recent advances in formulations, current challenges and possible hypotheses concerning the use of such theranostics across the BBB.[LM1]

Introduction

The BBB is a unique barrier that regulates and controls the selective and specific transport of both exogenous and endogenous materials to the brain. Because of its specific structure, only fat-soluble molecules, anesthetics, alcohol and those compounds with a low molecular mass (<400–500 Da) can pass directly through the capillary walls [1]. Apart from these passive elements of the BBB, there are also enzymes on the lining of the cerebral capillaries that destroy unwanted peptides and other small molecules in the blood as it flows through the brain. The barrier located at the brain blood capillaries is formed of two parts (Figure 1): in the first, endothelial cells comprise the walls and are sealed together at their edges by tight junctions (TJ) that form a key component of the barrier; in the second part, these capillaries are enclosed by the flattened ‘end-feet’ of astrocyte cells.

Currently, delivering therapeutic agents to the brain is a major challenge. The possible potential mechanisms involved in crossing the BBB (Figure 2) include: (i) transmembrane

© 2013 Elsevier Ltd. All rights reserved.

Corresponding author: Nair, M.P. (nairm@fiu.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

passive diffusion (TMPD). This favors molecules with a low molecular mass and a high degree of lipid solubility [2]. However, the sequestration from drug forms that too lipid soluble can also cause toxicity [3]; and (ii) use of transporter proteins. Although as a general rule, only lipid-soluble molecules can cross from the blood to the brain, different molecules can gain access to the brain via certain endogenous transport systems within the BBB. Thus, an alternative approach is to make drug molecules that 'ride' on the natural transporter proteins in the cerebral capillaries, so-called 'carrier-mediated transport' [LM2](CMT) or 'receptor-mediated transport' (RMT). In CMT, water-soluble brain nutrients, such as glucose, amino acids and nucleosides, cross the BBB via the GLUT1, LAT1 and MCT1[LM3] transporters. In RMT, certain large-molecule peptides or plasma proteins are selectively transported across the BBB by conjugating with ligands such as lactoferrin, transferrin and insulin [4]. RMT comprises three sequential steps: (i) receptor-mediated endocytosis at the luminal membrane; (ii) movement through the endothelial cytoplasm; and (iii) exocytosis of the peptide into the brain interstitial fluid [5]. Blood leukocytes such as monocytes and macrophages, and T cells can cross the BBB by chemotaxis, thereby modifying the functionality of TJs. In addition to CMT and RMT, adsorptive-mediated transport is also a type of endocytosis. For example, owing to electrostatic interactions, cationized ligand-conjugated nanoparticles (NPs) use adsorptive-mediated transport (AMT) to enter the brain. Tight TJ modulation results in selective aqueous diffusion across paracellular junctions in the BBB [6].

The use of nanotechnology-based image-guided drug delivery to the brain

Currently, several noninvasive image-guided modalities have been used in biomedical and clinic settings, including MRI, CT, PET, SPECT, electron microscopy, autoradiography, optical imaging and US [7]. Among these, PET and optical imaging are regarded as quantitative or semiquantitative imaging modalities, whereas CT and MRI are normally used for anatomical imaging [8]. Although the intact structure of the BBB inhibits the outer source materials entering the brain and CNS system, nanocarriers with appropriate surface characterization or conjugated with different types of ligand are a promising 'Trojan horse' approach for the release of therapeutics into tissues and neuronal cells, especially in CMT- and RMT mediated drug delivery and endocytosis [9]. Thus, the concept of 'theranostics' (diagnosis with therapy) can aid in the deliver of drugs into the CNS and across the BBB in a more accurate and direct way. In this review, we summarize and discuss the current status of image-guided drug delivery across the BBB.

Applications of image-guided drug delivery through the BBB by nanotechnology

With the aid of drug delivery image guided by NPs with high specificity and multifunctionality, drug and diagnostic molecules can be delivered to the brain across the BBB as personal medicine, enabling considerable progress to be made in the understanding and treatment of CNS diseases. These nanoscaled carriers can also minimize the exposure of healthy tissues to drugs because of nanotechnologically altered pharmacokinetics (PK) and biodistribution of the drugs and promotion of enhanced crossing of the BBB [10,11].

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Image-guided TMPD, CMT, RMT and AMT

Passive diffusion is the simplest method for CNS transport and depends upon the concentration gradient, molecular mass and charge of the drug. In addition to the molecular mass being <400 Da, diffusion of a drug also depends on the volume of drug and its charge. Generally, small, nonionic, lipid-soluble molecules penetrate easily across the BBB, whereas larger, water-soluble and/or ionic molecules are less likely to exhibit passive diffusion. For drugs to be delivered across the BBB, they have to be modified into lipophilic forms or attached to carriers that enable the drug to cross the BBB. However, few studies have focused on this pathway[LM4].

Apart from passive diffusion, CMT, RMT and AMT are also major routes for NP delivery across the BBB. The CMT drug delivery approach depends in large part on the transport affinity and capacity of BBB carriers [12]. For neurological molecular imaging applications, low-molecular mass probes are most likely to find their way into brain via passive diffusion or CMT. RMT across the BBB occurs because of the high specificity of brain endothelial transferrin and insulin [LM5][13]. Researchers have used a chimeric transferrin receptor monoclonal antibody (TfRMAb) with high activity for the mouse transferrin receptor (TfR) as a therapeutic fusion protein for BBB drug delivery by the RMT pathway [14,15]. In addition, cell-penetrating peptides (e.g. TAT-derived peptides and cationic albumin proteins) have been commonly used to enhance brain drug delivery via AMT [16]. AMT-mediated drug delivery to the brain relies on the interaction of a ligand with moieties expressed at the luminal surface of cerebral endothelial cells [17]. A wide range of CNS drugs, including therapeutic peptides, proteins and genes, can gain entry into the brain via NP carriers. The functionalization of NPs was the first step towards nanoscale drug delivery systems, although the mechanism of NP transport has not yet been fully elucidated.

MRI and FUS image-guided BBB breakthroughs using functional NPs

MRI is one of the most powerful noninvasive clinical imaging modalities used to visualize detailed internal structures with high spatial resolution. MRI makes use of the property of nuclear magnetic resonance (NMR) to image nuclei of atoms inside the body. It can provide a complete 3D anatomical neuroimage of the treatment area (coronal, axial and sagittal), including the brain. In addition, the appearance of blood vessels, tumors or inflammation can be enhanced by MRI resolution and increased further by using NPs as a contrast reagent. Magnetic NPs (MNPs) are of considerable interest as contrast agents for MRI and carriers for drug delivery [18]. However, because US can cause physically reversible disruption to TJs [19], the focus US (FUS) technique, which is a combination of MRI and US techniques, can concentrate acoustic energy on a focal spot, providing MRI-guided targeting and real-time temperature mapping [20].

Nanotechnology has been used for the delivery of therapeutic drugs through TJs by changing the microenvironment of the brain [21]. For example, liposomes can prolong the clearance time and improved structural stability[LM6]. It has been shown that the BBB can be circumvented by lipid-mediated transport [22,23]. In work by Heneweer *et al.*, magnetic liposomes were phagocytosed by human monocytes, and the application of a magnetic field induced the transmigration of magnetic monocytes across the BBB for cytosolic delivery to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

glioblastoma [24]. Zainulabedin *et al.* showed that delivery of the drug AZTTP using magnetic liposomes increased the effectiveness of treatment for neuroAIDS and could reduce the risk of developing drug-resistant viral strains in the brain by application of an external magnetic field [25]. In this work, AZTTP was bound to MNPs through electrostatic forces. Using an external magnetic force, drug-loaded MNPs were dragged through the BBB, significantly decreasing the level of HIV virus [25]. In addition, Koffie *et al.* prepared biodegradable nanocarrier systems comprising poly(*n*-butyl cyanoacrylate) dextran (PBCA) polymers coated with polysorbate 80 to deliver BBB-impermeable molecular imaging probes into mouse brains for targeted molecular neuroimaging of Alzheimer's disease (AD). The PBCA NP-based multiphoton optical imaging showed that FUS can induce a localized and reversible opening of the BBB, and that MRI can be applied as a precise tool to monitor local BBB disruption [26]. Lui and colleagues combined the use of FUS and magnetic targeting to deliver synergistically therapeutic MNPs across the BBB to treat CNS pathologies (Figure 3) [27]. Their work showed that synergistic targeting and MRI image monitoring are powerful techniques for the delivery of macromolecular chemotherapeutic agents into the CNS under the guidance of MRI [27].

Engineering antibodies to cross the BBB

It is well known that few antibodies can penetrate the BBB because of their molecular volume and mass. Encouraged by tumor diagnosis and treatment, engineered antibodies have been applied in the CNS [28,29]. In recent studies, Atwal, Yu and colleagues reported the design of an anti-TfR antibody that had two targets [9,30]. The first was β-secretase 1, which is a target for drugs to treat AD, and the second target for the transferrin receptor. By clinging to the transferrin receptor, the antibody was transported into the brain, where it was able to act against β-secretase 1. This double-duty antibody performed well in mouse models of AD [9,30]. Meanwhile, Feng and colleagues developed a series of antibody-coupled PEGylated liposomes (immunoliposomes) for receptor-mediated delivery of various therapeutics, including nucleic acids and drug molecules, to the brain [31]. As a protein, an antibody can ‘rid’ on the bilayer of liposome, which display dual role of targeting, therapy and pose its immunogenic effect[LM7].

Yu and Watts applied rat peptidomimetic RI7-217 monoclonal antibodies (mAb) to target peptide transcytosis systems through the mouse BBB *in vivo* by using transferrin receptor mediation [32]. O'Reilly and Hynynen demonstrated a MRI-targeted FUS-induced disruption of BBB, and then intravenously administered a dopamine D4 receptor-targeting antibody, which crossed the BBB and recognized its antigens. They could monitor the extent of BBB disruption by using MRI [33]. This novel technology could be useful in delivering macromolecular therapeutic or diagnostic agents to the CNS. In patients with AD, transcranial FUS-based MRI-guided FUS [LM8]was introduced as a diagnostic and therapeutic system to enhance the permeability of the BBB. MRI image-guided FUS was then established to deliver anti-Aβ antibodies to the brain in such patients [34].

Image-guided transfer across the BBB using intranasal administration

The intranasal delivery of drugs, including peptides, shows great promise for the successful delivery of drugs across the BBB. Intranasal administration is a so-called ‘bypassing’

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

strategy for crossing the BBB and might be an option for the delivery of large regulatory proteins [35].

In work by Wen *et al.*, an intranasal administration strategy was combined with nanotechnology to enhance the target effect on the brain. In this research, the lectin of odorranalectin (OL) was conjugated to the surface of poly(ethylene glycol)-poly(lactic-co-glycolic acid) (PEG-PLGA) NPs for nasal administration. The resulting tissue distribution of OL-modified NPs (OL-NP) demonstrated that intranasal administration resulted in better brain targeting efficiency compared with intravenous injection by fluorescence imaging [36]. Meanwhile, in a study by Kumar *et al.*, a nanoemulsion technique was used for targeting the brain with risperidone. *In vivo* gamma scintigraphy showed that the brain:blood uptake ratio following nasal administration was higher in the rat brain compared with that achieved by intravenous injection [37].

Multiple probe approaches to biomedical imaging of the brain using nanotechnology

PET and SPECT are noninvasive image modalities that have been used to make significant contributions to the understanding of brain function. Brain PET images generally reflect regional cerebral metabolism, whereas SPECT provides not only the localization of acute strokes, but can also direct thrombolysis during the postcerebrovascular accident period. PET and SPECT are gamma ray nuclear medicine-imaging techniques that can produce 3D images of general anatomy or the structure of organs [38]. In modern scanners, PET 3D images can be achieved using a CT X-ray of a patient simultaneously. PET imaging has been applied in the field of cancer detection and neuroscience. The major advantages of SPECT and PET over other modalities (e.g. optical and MRI) are their much higher sensitivity (picomolar level), quantity [LM9] , and nontissue penetration limitation [LM10] . However, one disadvantage is that the resolution (! 1 mm) of either SPECT or PET is not as high as that of other imaging modalities, such as MRI [39].

Instruments for producing dedicated brain-associated images have undergone significant improvements in the spatial resolution of tomography brain-imaging systems in nuclear medicine. To obtain more accurate information inside brain tissue, a multiple probe technique has been introduced into brain images. With the combination of PET and CT, the major inability of PET to provide anatomical information is overcome, and this technique can be used in the clinic for localization of metabolic abnormalities[LM11] . Although MRI can provide significant information at a soft-tissue level, it cannot provide insight into the physiology and/or pathology at the molecular level. The hybrid PET–MRI system provides the anatomical and structural description of MRI simultaneously with the quantitative capabilities of PET [7,40].

Imaging modalities such as CT and PET have been applied sequentially in the diagnosis and staging of disease and in monitoring the effects of therapy for several years, with PET offering high sensitivity and the ability to measure picomolar amounts of a PET radiopharmaceutical in a tissue. With 3D PET images, establishing a region of interest (ROI) and establishing the location of the organs or tissues in an image is vital. Given that the anatomic localization of functional abnormalities seen on PET scans can be affected by a lack of detail, the fusion images resulting from PET–CT or PET–MRI can provide high-

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

resolution anatomical details on the same image, providing new avenues for diagnostics and quantization at a higher spatial resolution and for more accurate regional analysis within the brain [8,41]. For example, cerebrovascular disorders, including transient ischemic attacks, stroke, subarachnoid hemorrhage and arteriovenous malformation, have been evaluated using a combined PET/CT scanner. This device provides accurately aligned anatomical and functional images for a patient from a single scanning session. Scintigraphic findings of hypoperfusion in acute stroke precede those of CT and MRI. Typically, 8 h after onset of acute stroke, 90% of SPECT images will demonstrate a perfusion abnormality, whereas only 20% of CT scans will be positive [13,42[LM12]].

Fluorescence offers an interesting method to monitor fundamental features of cellular organization in real time. Fluorescence molecular tomography (FMT) imaging has proven to be an invaluable tool for drug development and PK studies. It has been applied in studies of cancer detection and protein PK [43,44]. As a powerful functional and molecular imaging technique, FMT provides a resolution of approximately 1–5 mm and an imaging depth at the organ level of approximately 5–40 mm. One advantage of NP-based FMT is the enhanced ability to study and track molecular events within neurons and glia from seconds to minutes. A variety of NIR fluorescent image agents has been used for *in vivo* imaging [45]. By using intravital fluorescence microscopy, the penetration and accumulation of nanomedicines in the brain can be demonstrated. Researchers have also applied dual-purpose NPs to image neuroblastoma cells by both fluorescence imaging and MRI imaging on neuroblastoma cell surfaces [46]. Previous work showed the thermal threshold for selective and temporary opening of the BBB using MRI temperature information that came from thermal images. In addition MRI, iron oxide and gold NPs can also be used as detective images, owing to their high physical contrast properties [47]. Bonoiu et *al.* reported the local synthesis of chemoattractive factors in gliomas and that inflammatory cells can pass through the BBB [LM13][48]. Table 1 summarizes the main image modalities applied to the brain and CNS.

The merger of two or more molecular imaging technologies is motivated by the desire to measure multiple molecular targets simultaneously. Developing simultaneous 3D images on display and analysis from multiple modalities, such as MRI, PET and fluorescence, can provide complementary anatomical information about brain because of the capacity of nanomaterials on its functional surface[LM14]. A general algorithm for defining the affine transformation between two equivalent point ensembles can be adapted by means of a simple fiducial arrangement. If the native atlas planes are spaced at 2-mm intervals, this allows for an infinite number of angulations and axial offsets in the 2D region-of-interest templates in the brain.[LM15] Overall, simultaneous PET–MRI even replaces PET–CT as the molecular multimodality image platform of choice, opening a new avenue for the combinatory use of hybrid detection techniques.

A systematic approach to image-guided drug delivery to the brain requires mechanisms for targeting, delivery, activation and monitoring of the process in the CNS. Various imaging techniques have been applied, and the nanotechnology-based applications of theranostics range from the noninvasive assessment of the biodistribution and the target site accumulation of loaded drugs to the visualization of drug distribution and drug release at the target site in the brain. The implementation of therapies and surgical interventions using

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

imaging technologies will be an important tool for accelerating the transition towards molecular and personalized medicine and, therefore, to combat CNS disease.

However, there are still some challenges regarding the use of nanotechnology and imaging modalities in the brain: (i) analytic imaging methods, including penetration, quantitative assays and resolution. Owing to the specific tissue structure of the brain, the selection of proper imaging with good penetration is essential and PET– SPECT is an option. MRI is a good choice owing to its high resolution in soft tissue in the brain. With the 2D and 3D structures obtained of the brain, the region of interest for the delivery of drugs can be easily located, making quantitation feasible and more accurate. However, quantitative assays still need to be improved in all modalities. Although fluorescence, especially in NIR, has an important role in slide tissue analysis because of its high resolution and low cost, its low penetration limits its noninvasive application. (ii) Biohazards: although most of the modalities are described as being ‘noninvasive’, the possible hazard from particles or/and modalities cannot be ignored (e.g. toxic composition, CT, etc.). These problems can be overcome by selective choosing of materials and modalities. (iii) Cost estimation: although MRI can provide high-resolution images of the brain, its high maintenance cost is still a burden for most researchers. However, ferrous MNPs (FMNPs) might be the answer. Owing to their unique properties, drugs binding on FMNPs can be dragged by an external magnetic field across the BBB. If the surface can be coated with a layer of rare metal (e.g. gold or silver), the superconductivity of the particles of rare metal can be used to control the surface charge and drug binding and/or release. By their incorporation with MRI and/or PET/ fluorescent modalities, FMNPs could be an ideal nanotheranostic platform for drug delivery to the brain.

Concluding remarks

The main aim of image-guided targeted drug delivery to the CNS and brain is to optimize the therapeutic ratio, ideally through optimized targeting, PK, pharmacodynamic and reduced toxicity of nanodrugs. The full implementation of image-guided drug delivery to the brain requires that drugs can be imaged locally or activated at the targeted site, which can be achieved by using functional nanomaterials. Given that imaging is inherent to image-guided drug delivery to the brain, its application post therapy could provide early indication of the response to therapy for brain tumors or drug addiction. Given the broad application of imaging modalities, combining noninvasive imaging with robust nanotechnology could be a future direction for the targeted delivery of drugs to the CNS and brain. The application of MRI, FMT in the NIR range and their combined use with PET, SPECT, CT and US, can provide images not only at a tissue level, but also at the molecular level in brain research for real-time tracking[LM16].

Acknowledgments

This work was supported by funding from the National Institute of Health (NIH grant 1R01DA027049).

References

1. Kumar A. HIV and substance abuse. Curr HIV Res. 2012; 10:365–365. [PubMed: 22762418]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

2. Zhang X, et al. *In vitro* and *in vivo* investigation of dexibuprofen derivatives for CNS delivery. Acta Pharmacol Sin. 2012; 33:279–288. [PubMed: 22301864]
3. Banks W. Characteristics of compounds that cross the blood–brain barrier. BMC Neurol. 2009; 9(Suppl. 1):S3. [PubMed: 19534732]
4. Xu G, et al. Bioconjugated quantum rods as targeted probes for efficient transmigration across an *in vitro* blood–brain barrier. Bioconjug Chem. 2008; 19:1179–1185. [PubMed: 18473444]
5. Chu P, et al. Pharmacodynamic analysis of magnetic resonance imaging-monitored focused ultrasound-induced blood–brain barrier opening for drug delivery to brain tumors. BioMed Res Int. 2013; 2013:627496. [PubMed: 23607093]
6. Mahajan SD, et al. Methamphetamine alters blood–brain barrier permeability via the modulation of tight junction expression: implication for HIV-1 neuropathogenesis in the context of drug abuse. Brain Res. 2008; 1203:133–148. [PubMed: 18329007]
7. Hofmann M, et al. MRI-based attenuation correction for PET/MRI: a novel approach combining pattern recognition and atlas registration. J Nucl Med. 2008; 49:1875–1883. [PubMed: 18927326]
8. Ding H, Wu F. Image-guided biodistribution of drugs and drug delivery. Theranostics. 2012; 2:1037–1039. [PubMed: 23227120]
9. Atwal JK, et al. A therapeutic antibody targeting BACE1 inhibits amyloid-β production *in vivo*. Sci Transl Med. 2011; 3:84ra43.
10. Yang H. Nanoparticle-mediated brain-specific drug delivery, imaging, and diagnosis. Pharm Res. 2010; 27:1759–1771. [PubMed: 20593303]
11. Ding H, Wu F. Images guided biodistribution and pharmacokinetic studies of theranostics. Theranostics. 2012; 2:1040–1053. [PubMed: 23227121]
12. Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev. 2012; 64:213–222.
13. Wu, F.; Ding, H. Antibody-Mediated Drug Delivery Systems: Concepts, Technology and Applications. John Willey & Sons; 2012. mAb-mediated dds for lymphatic targeting treatment; p. 169-190.xxxx[LM17], eds
14. Boado RJ, et al. Engineering and expression of a chimeric transferrin receptor monoclonal antibody for blood–brain barrier delivery in the mouse. Biotechnol Bioeng. 2009; 102:1251–1258. [PubMed: 18942151]
15. Pardridge WM. Biopharmaceutical drug targeting to the brain. J Drug Target. 2010; 18:157–167. [PubMed: 20064077]
16. Johnson, R., et al. Therapeutic applications of cell-penetrating peptides. In: Langel, Ü., editor. Cell-Penetrating Peptides. Humana Press; 2011. p. 535-551.
17. Fu B. Experimental methods and transport models for drug delivery across the blood-brain barrier. Curr Pharm Biotechnol. 2012; 13:1346–1359. [PubMed: 22201587]
18. Hynynen K. Focused ultrasound for blood–brain disruption and delivery of therapeutic molecules into the brain. Expert Opin Drug Deliv. 2007; 4:27–35. [PubMed: 17184160]
19. Palmowski M, et al. Molecular profiling of angiogenesis with targeted ultrasound imaging: early assessment of antiangiogenic therapy effects. Mol Cancer Ther. 2008; 7:101–109. [PubMed: 18202013]
20. Burgess A, et al. Targeted delivery of neural stem cells to the brain using MRI-Guided focused ultrasound to disrupt the blood– brain barrier. PLoS ONE. 2011; 6:e27877. [PubMed: 22114718]
21. Capaldo CT, Nusrat A. Cytokine regulation of tight junctions. Biochim Biophys Acta. 2009; 1788:864–871. [PubMed: 18952050]
22. Peng A, et al. PEGylation of a factor VIII–phosphatidylinositol complex: pharmacokinetics and immunogenicity in hemophilia a mice. AAPS J. 2012; 14:35–42. [PubMed: 22173945]
23. Meyers JD, et al. Nanoparticles for imaging and treating brain cancer. Nanomedicine. 2013; 8:123–143. [PubMed: 23256496]
24. Heneweer C, et al. Liposomes and inorganic nanoparticles for drug delivery and cancer imaging. Ther Deliv. 2012; 3:645–656. [PubMed: 22834408]
25. Zainulabedin MS, et al. Magnetic nanoformulation of azidothymidine 5′-triphosphate for targeted delivery across the blood–brain barrier. Int J Nanomed. 2010; 5:157–166.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

26. Koffie RM, et al. Nanoparticles enhance brain delivery of blood–brain barrier-impermeable probes for in vivo optical and magnetic resonance imaging. Proc Natl Acad Sci U S A. 2011; 108:18837–18842. [PubMed: 22065785]
27. Liu HL, et al. Magnetic resonance monitoring of focused ultrasound/magnetic nanoparticle targeting delivery of therapeutic agents to the brain. Proc Natl Acad Sci U S A. 2010; 107:15205–15210. [PubMed: 20696897]
28. Ding H, et al. Non-invasive tumor detection in small animals using novel functional pluronic nanomicelles conjugated with anti-mesothelin antibody. Nanoscale. 2011; 3:1813–1822. [PubMed: 21365120]
29. Lichota J, et al. Macromolecular drug transport into the brain using targeted therapy. J Neurochem. 2010; 113:1–13. [PubMed: 20015155]
30. Yu YJ, et al. Boosting brain uptake of a therapeutic antibody by reducing its affinity for a transcytosis target. Sci Transl Med. 2011; 3:84ra44.
31. Feng B, et al. Delivery of sodium borocaptate to glioma cells using immunoliposome conjugated with anti-EGFR antibodies by ZZ-His. Biomaterials. 2009; 30:1746–1755. [PubMed: 19121537]
32. Yu, YJ.; Watts, RJ. Developing therapeutic antibodies for neurodegenerative disease. Neurotherapeutics. 2013. http://dx.doi.org/10.1007/s13311-013-0187-4
33. O'Reilly MA, Hynynen K. Ultrasound enhanced drug delivery to the brain and central nervous system. Int J Hyperthermia. 2012; 28:386–396. [PubMed: 22621739]
34. Jordão JF, et al. Antibodies targeted to the brain with image-guided focused ultrasound reduces amyloid-β plaque load in the TgCRND8 mouse model of Alzheimer's disease. PLoS ONE. 2010; 5:e10549. [PubMed: 20485502]
35. Tan ML, et al. Recent developments in liposomes, microparticles and nanoparticles for protein and peptide drug delivery. Peptides. 2010; 31:184–193. [PubMed: 19819278]
36. Wen Z, et al. Brain targeting and toxicity study of odorranalectin-conjugated nanoparticles following intranasal administration. Drug Deliv. 2011; 18:555–561. [PubMed: 21812752]
37. Kumar M, et al. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm. 2008; 358:285–291. [PubMed: 18455333]
38. Zhen Z, Xie j. Development of manganese-based nanoparticles as contrast probes for magnetic resonance imaging. Theranostics. 2012; 2:45–54. [PubMed: 22272218]
39. Luk BT, et al. Lipid- and polymer-based nanostructures for cancer theranostics. Theranostics. 2012; 2:1117–1126. [PubMed: 23382770]
40. Zhou Y, et al. Radiolabeled Cyclic RGD peptides as radiotracers for imaging tumors and thrombosis by SPCET. Theranostics. 2011; 1:58–82. [PubMed: 21547153]
41. Nie Y, et al. Cholesterol derivatives based charged liposomes for doxorubicin delivery: preparation, in vitro and in vivo characterization. Theranostics. 2012; 2:1092–1103. [PubMed: 23227125]
42. Sobhani A, et al. Narrowband photodetection in the near-infrared with a plasmon-induced hot electron device. Nat Commun. 2013; 4:1643. [PubMed: 23535664]
43. Ding H, et al. Bioconjugated PLGA-4-arm-PEG branched polymeric nanoparticles as novel tumor targeting carriers. Nanotechnology. 2011; 22:165101. [PubMed: 21393821]
44. Wu F, et al. Noninvasive real-time fluorescence imaging of the lymphatic uptake of BSA-IRDye 680 conjugate administered subcutaneously in mice. J Pharm Sci. 2012; 101:1744–1754. [PubMed: 22262501]
45. Wu F, et al. Fluorescence imaging of the lymph node uptake of proteins in mice after subcutaneous injection: molecular weight dependence. Pharm Res. 2012; 29:1843–1853. [PubMed: 22373666]
46. Hu K, et al. Lactoferrin-conjugated PEG–PLA nanoparticles with improved brain delivery: *in vitro* and *in vivo* evaluations. J Control Release. 2009; 134:55–61. [PubMed: 19038299]
47. Ding H, et al. Gold nanorods coated with multilayer polyelectrolyte as contrast agents for multimodal imaging. J Phys Chem C. 2007; 111:12552–12557.
48. Bonoiu AC, et al. Nanotechnology approach for drug addiction therapy: gene silencing using delivery of gold nanorod-siRNA nanoplex in dopaminergic neurons. Proc Natl Acad Sci U S A. 2009; 106:5546–5550. [PubMed: 19307583]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

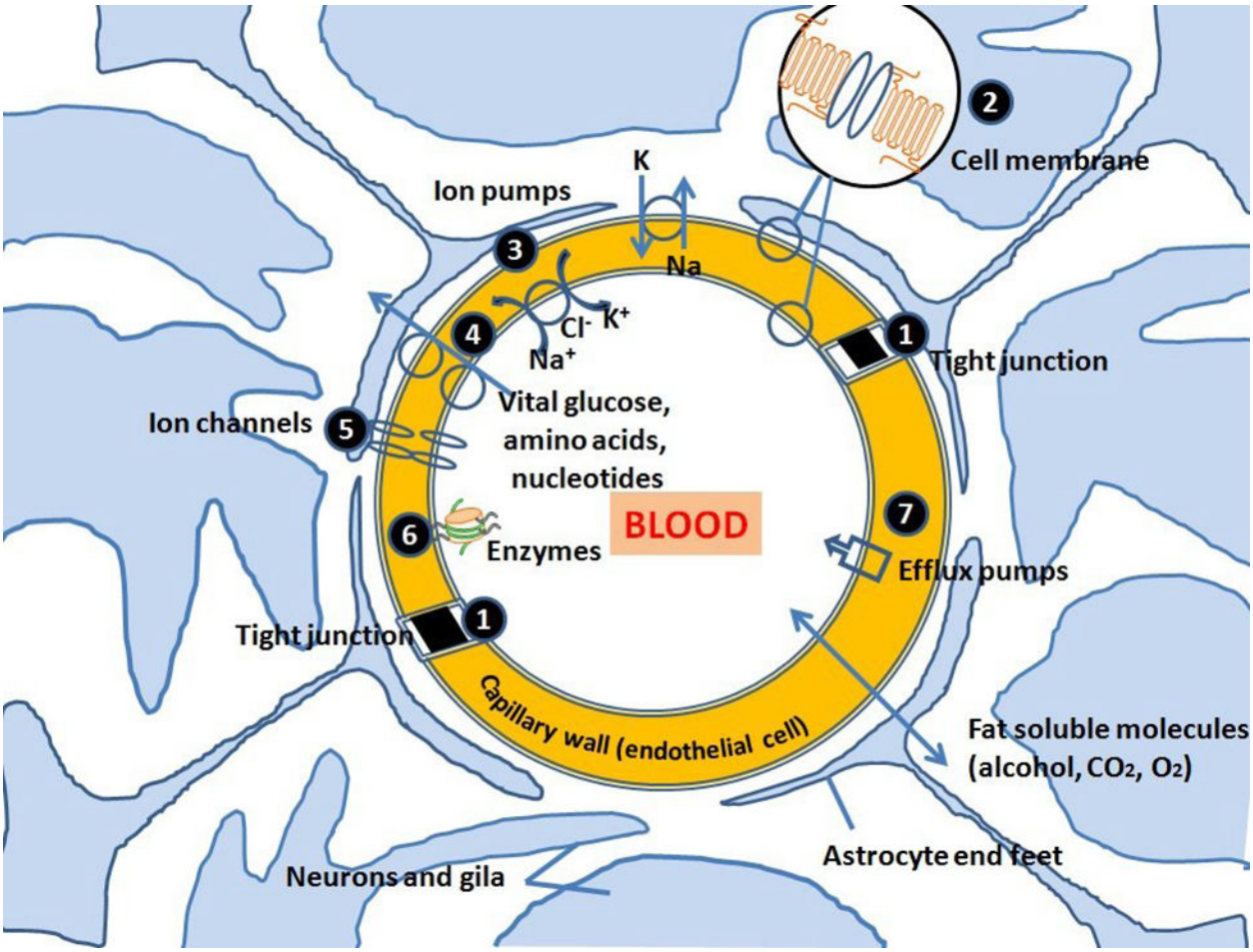

Figure 1.

[LM18]A cerebral capillary enclosed in astrocyte end-feet. Characteristics of the blood-brain barrier (BBB) are indicated: **(a)** tight junctions (TJs) that seal the pathway between the capillary (endothelial) cells; **(b)** the lipid nature of the cell membranes of the capillary wall makes it a barrier to water-soluble molecules; **(c–e)** represent some of the carriers and ion channels in the BBB; **(f)** the 'enzymatic barrier' that removes molecules from the blood; **(g)** the efflux pumps that extrude fat-soluble molecules that have crossed into the cells.

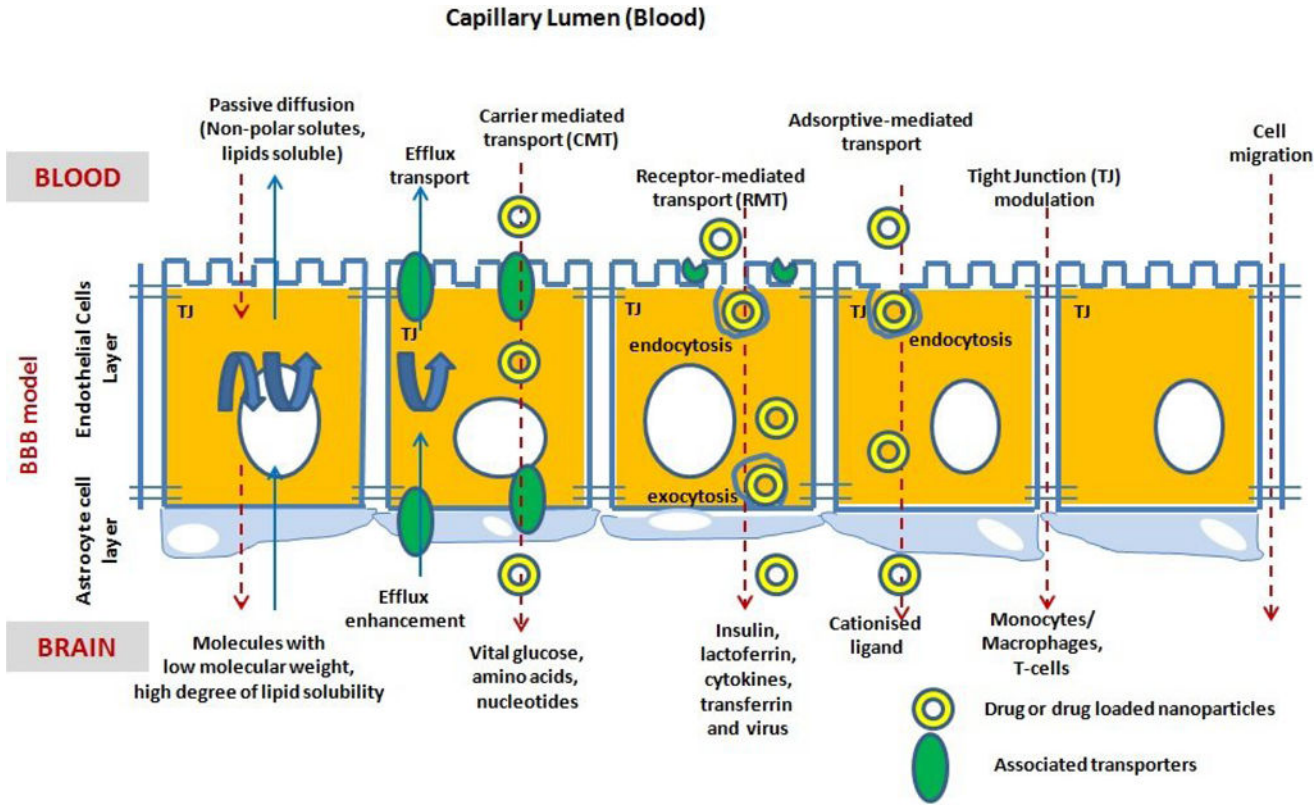

Figure 2.

[LM19]Potential transport mechanisms across the blood–brain barrier (BBB). Diffusion and active transport are the main transport mechanisms.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

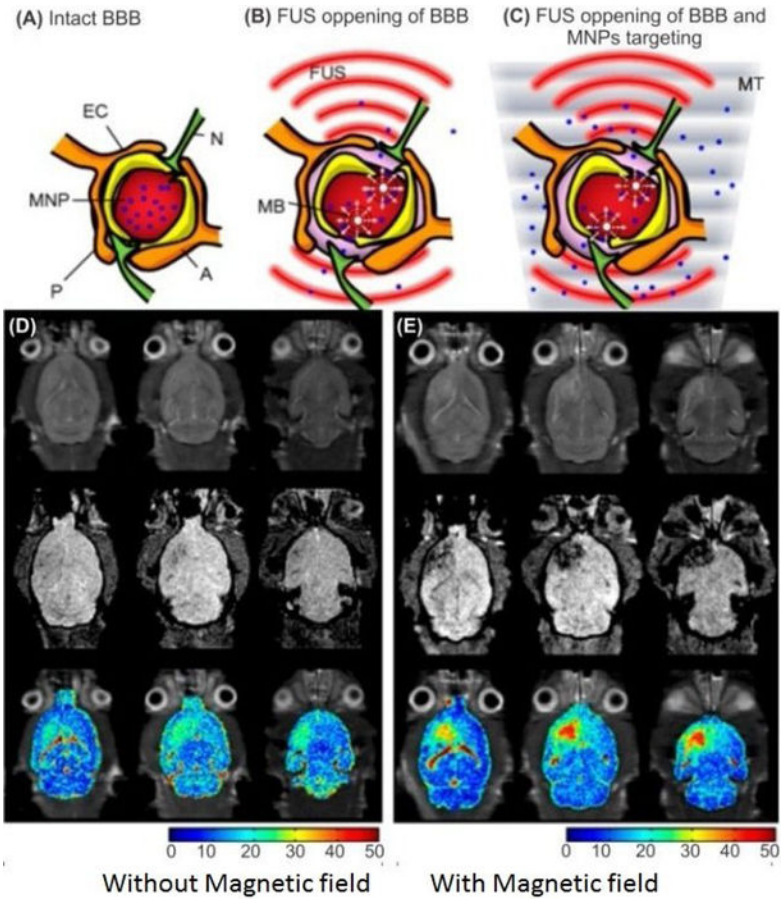

Figure 3.

Magnetic resonance image-guided focused ultrasound (MRIgFUS) drug delivery across the blood–brain barrier (BBB) using polymer-coated magnetic nanoparticles (MNPs) conjugated with epirubicin. **(a)** Intact central nervous system (CNS) capillaries. **(b)** Disruption of the BBB through activation of microbubbles (MBs) by FUS, enhancing the passive influx of therapeutic MNPs. **(c)** Active delivery of therapeutic MNPs to the brain through the use of combined magnetic targeting (MT) with FUS. **(d)** *In vivo* imaging of MNP distribution in the brain using FUS alone. **(e)** *In vivo* imaging of the distribution of MNPs in the brain using FUS and MT 6 h post treatment. Abbreviations: A, astrocyte; EC, endothelial cell; N, neuron; P, pericyte. Reproduced, with permission, from [27].

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 1

Summary of the main imaging modalities applied to the brain and CNS[a]

Acronym	Radiation type	Spatial resolution	Scanning time	Sensitivity (Mol/L)	Quantity of contrast agent	Biohazards	Summary and comments
MRI	Radiowaves	25–100!μ micro; or 1 mm [46]	30–40 min (brain, knee, spine and shoulder); 60–80 min (prostate and breast)	10^{-3}–10^{-5}	! g to mg Anatomical application!	Noninvasive	High resolution, morphological imaging and good for soft tissues
US	None	Poor	~5–10 min	N/A	Not applicable	Noninvasive and nonharmful	Can combine with other modalities
PET	High-energy gamma rays	1–2 mm	30–60 min (brain and oncology); 2 h (complete scan)	10^{-11}–10^{-12}	ng, quantitative or semi-quantitative	Noninvasive	Sensitive and quantitative, but needs cyclotron[LM20]
SPECT	High energy gamma rays	1–2 mm	40 min [54]	10^{-10}–10–$^{-11}$	ng, quantitative or semi-quantitative	Noninvasive	Many available probes
CT	X-rays	50-200 μ	15 min (without contrast), 30 min (with contrast), 60 min (cardiac CT)	N/A	Anatomical application	Can alter DNA	Good for bone and tumors, but not for soft tissues
FMT	Fluorescence	1–5 mm	10 s to min[LM21]	10^{-9}–10^{-12}(NIR) 10^{-15}–10^{-17} (bioluminescenc e) [55]	ng, quantitative or semiquantitativ e	Noninvasive and nonharmful	High sensitivity, but low penetration

[a] See [43,46,54,55[LM22]] for further information.