Chapter 7
Nano-engineering Nanoparticles for Clinical Use in the Central Nervous System: Clinically Applicable Nanoparticles and Their Potential Uses in the Diagnosis and Treatment of CNS Aliments

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Abstract Nano-engineering materials-based diagnosis and treatment of central nervous systems (CNS) ailments has significantly advanced with our deepened knowledge of the pathophysiology of the blood–brain barrier. Unlike other nanoparticle-based tissue engineering strategies, the use of nanoparticles in the CNS must be specifically engineered to circumvent or penetrate the blood–brain barrier, which selectively inhibits drugs and nanoparticles from infiltrating. Current research in the field of CNS nanoparticles has future applications in the fields of diagnostic imaging, drug delivery, specific drug targeting, and tissue regeneration. This chapter highlights some of the nano-engineering of these promising nanoparticle-based biomaterials and their applications in the diagnosis and treatment of brain and spinal cord disease.

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7.1 Introduction

While significant advances in our understanding of the pathophysiology of the central nervous system (CNS) have occurred, our diagnosis and treatment strategies of CNS ailments remain limited. Diagnosis is still challenging as small lesions in an eloquent region of the brain, or spinal cord can lead to significant deficits and large lesions that do not affect eloquent regions of the brain may not result in any clinically noticeable deficits or symptoms. Our ability to visualize these small lesions remains limited with current clinical imaging technology. While we have also made significant strides in our ability to offer therapeutic strategies, many of these agents cannot be applied systemically as they are inactivated with systemic administration, cannot cross the blood–brain barrier (BBB) [1, 2], are rapidly degraded in the circulatory system [3], or cause unacceptable systemic side effects [4]. Accordingly, CNS-targeted nanoparticles may be the answer to these barriers, improving the diagnosis and treatment of CNS disorders.

7.1.1 The Blood–Brain Barrier: A Physiological Barrier to Treatment

The blood–brain barrier (Fig. 7.1) is a physical and chemical barrier which protects the CNS and offers homeostasis. Formed from capillary endothelium, astrocytes, pericytes, and extracellular matrix, the BBB allows for highly controlled diffusion of essential compounds from the bloodstream into the CNS, such as water, lipid-soluble molecules, and gasses while restricting the entry of pathogenic organisms and other potentially harmful substances, including hydrophilic molecules >1 kDa and exogenous molecules. These functions are largely dependent on the presence of a variety of components, such as tight junctions which are highly selective in order

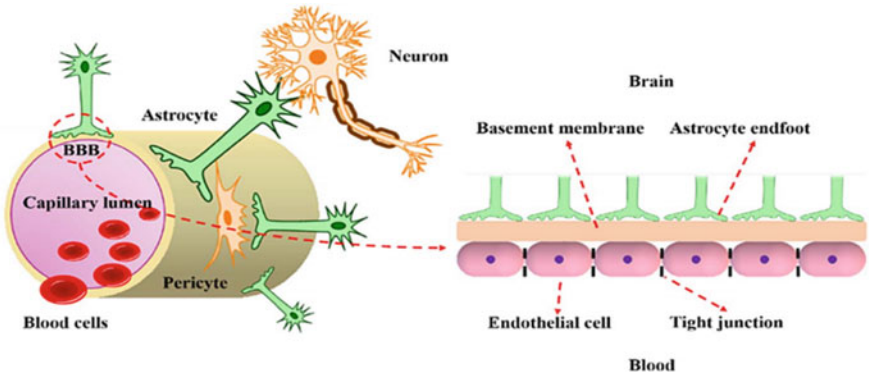

Fig. 7.1 Schematic of blood–brain barrier Adapted with permission from Zhou et al. [7]

to limit the passage of solutes, ATP-binding cassette transporters (ABC transporters) which actively pump xenobiotics out of the CNS [5], and endothelial cytochromes and enzymes, which degrade small-sized molecules [6].

Circumventing the BBB presents a standing challenge for the diagnosis and treatment of many CNS-related ailments. Over 95% of pharmaceuticals which could diagnose or treat CNS-related diseases cannot cross the BBB, and while many of these treatments have been successful in animal models of disease, they cannot be translated for human use due to failure of drug delivery [8, 9]. This is particularly challenging when repeated administration is required for sustaining a therapeutic dose [10].

Current delivery of CNS-specific therapeutics across the BBB can be categorized as physical, chemical, or biological and can be used for CNS-specific diseases. Physical delivery can be achieved by using transcranial drug delivery methods to pass drugs directly into the brain, physically trespassing the BBB. These methods involve neurosurgical procedures which can be accomplished via intracerebral implantation (Fig. 7.2a), intracerebral infusion (Fig. 7.2b), and convection-enhanced diffusion (Fig. 7.2c). Intracerebral infusion and intracerebral implantation are both able to bypass the BBB with physical penetration. However, studies have indicated that as the drug penetrates the brain tissue, the concentration of bioavailable drugs decreases significantly with each millimeter of tissue away from the site of injection or implant. By their definition, these methods are invasive and require the patient to undergo a surgical procedure [11].

Chemical-based drug delivery is based on causing a break in the BBB which allows drugs to penetrate through the tight junctions. This BBB disruption can occur by utilizing:

- Osmotic disruptors such as bradykinins
- Use of high-intensity ultrasound
- Introducing osmotic pressure or microbubbles.

These methods, while novel, are potentially harmful to patients as they may permanently damage the integrity of the BBB, allowing not only the targeted pharmaceutical but other potentially harmful substances to cross [7]. Biological-based drug delivery utilizes the targeting of a drug to a ligand which can bind to an endocytic receptor or lipophilic analog to improve BBB penetration or diffusion [12]. However, studies have shown that all these methods suffer from a range of limitations, including but not limited to lack of specificity, resulting in adverse effects on healthy tissues, and loss of bioavailable concentration, necessitating repeated exposure, which results in further adverse effects [10].

7.1.2 Nanoparticle-Based Delivery

Nanoparticles are small structures on the nanoscale (1–100 nm, see Chap. 1). They can be utilized to carry and deliver therapeutic agents in complex biological systems

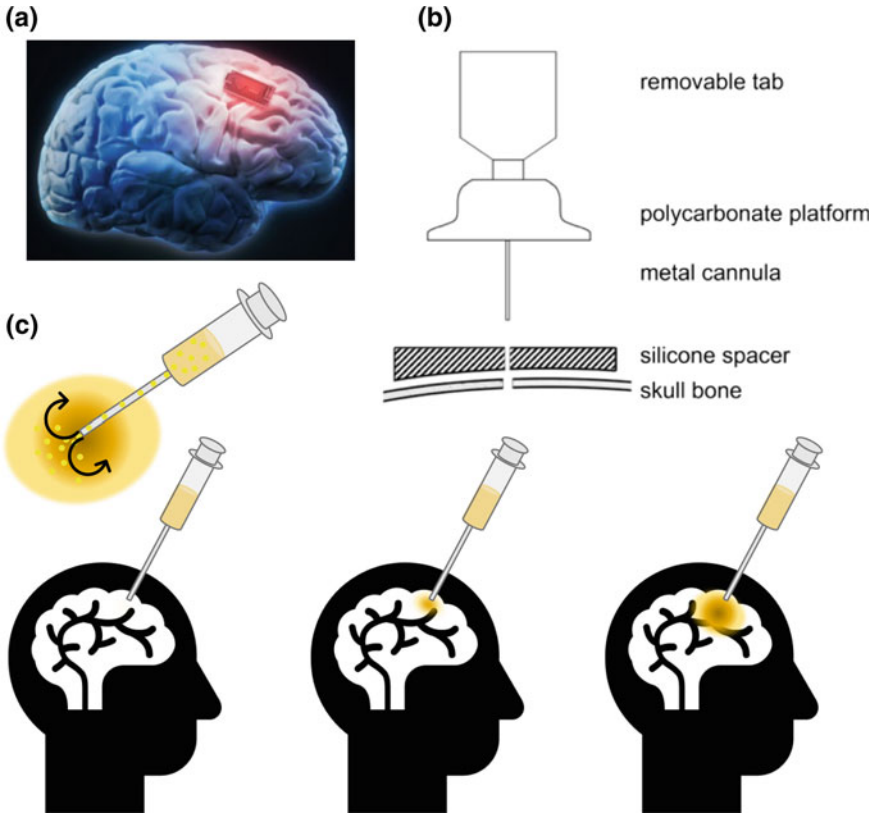

Fig. 7.2 Physical delivery methods through the BBB. **a** Intracerebral implantation: involves placement of the target drug or delivery system directly on the brain's surface. **b** Cannula for intracerebral infusion. This cannula would require surgical insertion through the skull bone to enter the brain. **c** Convection-enhanced diffusion: Using a pump, target drug is infused through a cannula inserted into the target with the addition of continuous positive pressure

as therapeutic nano-carriers. These carriers have been fabricated from many different materials and are highly customizable in regard to size, charge, and molecular properties [10]. Nanoparticles are the ideal molecules for CNS-specific drug delivery. Recent studies have focused on the creation of biodegradable nanoparticles which are able to increase therapeutic bioavailability, retention, and solubility of diagnostic and therapeutic agents. These agents can be encapsulated by or embedded within the surface of nanoparticles, which protects the drug from degradation and allows for extended release. Payload-carrying nanoparticles can be further modified with receptor-targeting ligands, which results in targeting of the whole system to specific tissues. Due to their versatility, nanoparticle-based delivery systems are currently being studied for CNS-related clinical applications in cancers, acquired immunodeficiency syndrome (AIDS), as well as non-CNS-related clinical applications such as non-CNS cancers, diabetes, malaria, and tuberculosis [10].

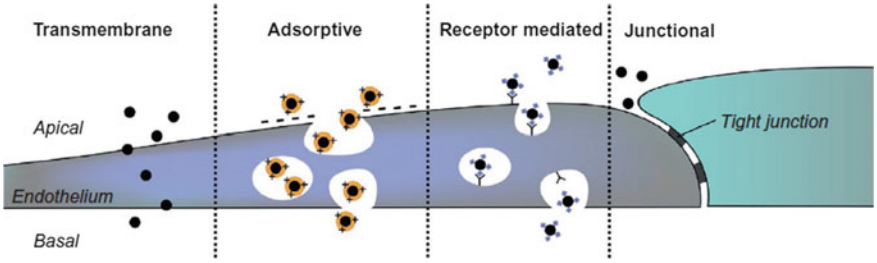

Fig. 7.3 Routes for movement of nanoparticles across the brain endothelium reproduced with permission from Male et al. [10]

Table 7.1 Summary of active and passive transport of nanoparticle-based CNS drug delivery

	Active transport			Passive transport
Mechanism	Receptor-mediated	Adsorptive	Carrier-mediated transport	Transmembrane
Targets	Ligands for receptors	Cationic nanoparticles	Ligands for transport proteins	Small lipophilic molecules < 400-500 Da
Examples	PBCA PLGA/PLA Transferrin-conjugated nanoparticles Liposomes	Liposomes	PLGA/PLA carbon quantum dots	Gold nanoparticles Sliver nanoparticles

Nanoparticle-based delivery of pharmaceuticals to the CNS offers many benefits when compared to traditional physical, chemical, and biological methods of cross-BBB delivery. Nanoparticles can offer a noninvasive, low-cost, and highly controlled method to load and release these targeted drugs across the BBB [10].

Transport across the BBB can both be passive or active. Passive transport is energy-independent and utilizes the process of passive diffusion. This is particularly useful for tumor cells due to the enhanced permeability and retention effect. In contrast, active transport requires the use of carriers at the expense of adenosine triphosphate (ATP) via a receptor and adsorption-mediated routes (Fig. 7.3). These differences, with examples of nanoparticles which will be further discussed below, are highlighted in Table 7.1.

7.2 Polymeric Nanoparticles

Polymeric nanoparticles (Fig. 7.4) are composed of natural or synthetic polymers and can be fabricated into nanoparticles that are suitable for CNS delivery.

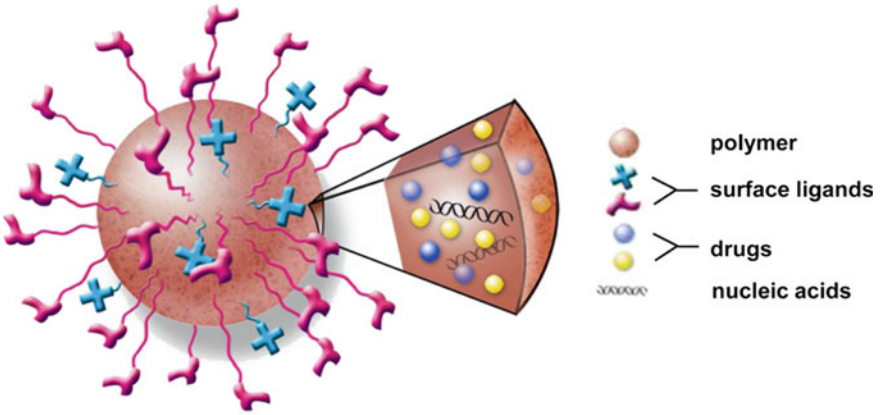

Fig. 7.4 Schematic of a functionalized polymeric nanoparticle. Reproduced with permission from Patel et al. [13]

These nanoparticles have been based on polysaccharides, proteins, amino acids, poly(ethylenimines), poly(alkylcyanoacrylates), poly(-methylidene malonates), and polyesters [13]. There are currently two polymeric-based nanoparticle drug delivery systems which are Food and Drug Administration (FDA) approved for clinical use:

1. Abdoscan®: An iron oxide and dextran-based nanoparticle used for diagnostic imaging of the liver and spleen [14].
2. Abraxane®: An albumin-based nanoparticle loaded with paclitaxel used in the treatment for breast cancer [15].

The basic structure of a polymeric nanoparticle is illustrated in Fig. 7.4. The drug, which could be a synthetic molecule, a peptide, or a nucleic acid in nature, is embedded within the walls of the polymer, while the surface is modified with a ligand, which is intended to deliver the nanoparticle to the area of interest. In the context of treatments of CNS ailments, the ligand would specifically target a component within the BBB. Systemic delivery of these nanoparticles across the BBB is possible because their surface can be so readily modified, relying on ligand surface-modification for receptor-mediated transcytosis or surface charge-modification for adsorptive-mediated transcytosis [13]. Unfortunately, these favorable characteristics are still restricted by potential toxicity, including both chemical toxicity determined by the purity and concentration of these nanoparticles, along with nano-toxicity resulting from particle size, shape, surface, and charge [16].

7.2.1 Poly(Butyl cyanoacrylate) Nanoparticles

First synthesized in 1995, poly(butyl cyanoacrylate) (PBCA, see Fig. 7.5) nanoparticles were the first polymer-based nanoparticle system studied to deliver drugs to

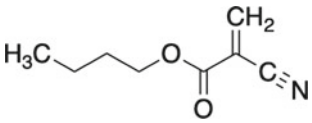

Fig. 7.5 Chemical structure of poly(butyl cyanoacrylate)

the CNS through the BBB [17]. PBCA nanoparticles were loaded with dalargin, an opioid peptide Leu-enkephalin with analgesic properties, coated with polysorbate 80, and delivered intravenously and orally. The results showed that these nanoparticles are able to achieve analgesia in the CNS of a mouse model [18]. Follow-up studies, using radiolabeled particles, demonstrated that in the absence of polysorbate-80 coating, there was a significant decrease in the number of PBCA nanoparticles that crossed the BBB [19]. PBCA nanoparticles coated by polysorbate-80 can also be loaded with fluorophores, antibodies, or magnetic contrast agents, with possible clinical applications in diagnostic imaging of the CNS [20]. However, non-specific permeabilization of the BBB, probably related to the toxicity of the carrier, caused mortality in mice, questioning the clinical application of this nanoparticle [16].

7.2.2 *Poly(Lactic-Co-glycolic Acid)/Poly(Lactic Acid) Nanoparticles*

Poly(lactic-*co*-glycolic acid)/poly(lactic acid) (PLGA/PGA)-based nanoparticles, like PBCA, have been in development since the 1990s, due to their promising biocompatibility and biodegradability [21]. Their chemical structures can be seen in Fig. 7.6. PLGA/PLA can be hydrolyzed by the body into lactic acid or glycolic acid, respectively, and metabolized by the Kreb's cycle [22]. PLGA has many current clinical uses such as suture material. PLGA/PGA nanoparticles of different sizes, size distribution, morphology, and ζ potential can be synthesized by controlling the parameters specific to the synthesis method employed [23]. PLGA/PLA nanoparticles can also undergo surface-modification with surfactants or polymers, or covalent conjugation with targeting ligands which can improve BBB penetration. This high degree of customization makes PLGA/PGA nanoparticles applicable to a wide range of treatments within the CNS [22].

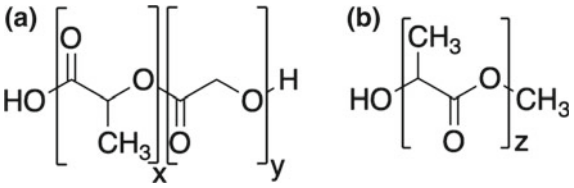

Fig. 7.6 **a** Chemical structure of poly(lactic-co-glycolic acid); x and y denote the number of unit repeats. **b** Chemical structure of poly(lactic acid): z denotes the number of unit repeats

Recent research has shown that PLGA nanoparticles conjugated with cyclopeptides can deliver zinc ions via endocytosis [24]. Curcumin-loaded PLGA nanoparticles conjugated with Tet-1 peptide have shown promising ability to cross the BBB in vitro and can potentially be applied for treating Alzheimer's dementia [25]. Paclitaxel-loaded PLGA nanoparticles have recently been produced by Lei et al. demonstrating excellent reproducibility and uptake in the mouse model [26].

7.2.2.1 PBCA/PLGA/PLA Nanoparticles as Drug Carriers for Alzheimer's Disease

Alzheimer's disease (AD) is a common and devastating type of dementia which is characterized by learning and memory impairment. There are about 4 million people living with dementia worldwide, and AD accounts for an estimated 60–80% of these cases [27].

Curcumin is a diarylheptanoid, which is a plant-based compound with biological activity against β-amyloid (Aβ) aggregate, shown in Fig. 7.7, which is the main component of neuronal amyloid plaques causing AD [28]. Unfortunately, curcumin has poor aqueous solubility and stability and is prone to oxidation and photodegradation. These properties make it a poor candidate for oral, systematic administration. PBCA nanoparticles embedded with curcumin have shown to improve the drug's photostability in a SH-SY5Y cell culture model [29]. The most promising of the nanoparticle curcumin carriers had sustained stability, with long-term (6 months) storage, while remaining bioactive [30]. In vitro experiments demonstrated that this system has the ability to destroy amyloid plaques [25], while in a mouse model, it was able to improve cue memory and lower amyloid plaque activity [31].

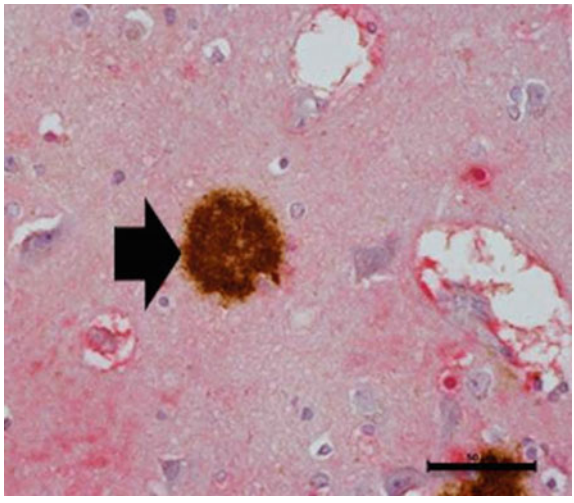

Fig. 7.7 Amyloid plaque, scale bar represents 50 μm Adapted from Mathur et al. [32]

7.2.3 Carbon Quantum Dots

Carbon quantum dots have been discovered in 2004 and are the newest member of the polymeric nanoparticle family discussed in this chapter [33]. Carbon quantum dots are a promising type of nanoparticle due to their low toxicity, small relative size, polymeric core, and the available surface functional groups [33]. These surface functional groups are particularly useful for conjugation with therapeutics for the purposes of drug delivery across the BBB [34, 35]. Quantum dots also have excellent photoluminescence, allowing for real-time tracking of BBB penetration shown in animal models [36].

Carbon quantum dots are nano-fabricated by either "top-down" or "bottom-up" synthesis. The top-down approach involves oxidizing double bonds from macromolecular starting materials such as raw carbon powder [37], while the bottom-up approach involves building carbon quantum dots from small monomeric units such as citric acid and amines using covalent hydrogen bonds [37]. Top-down carbon quantum dots are synthesized using raw carbon powder, which are then conjugated to transferrin and doxorubicin, making them a promising treatment agent for pediatric CNS neoplasms. Doxorubicin is a chemotherapeutic agent which is effective against many different cancers including breast, bladder, lymphoma, and sarcoma [38]. However, doxorubicin, like many chemotherapeutics, has side effects such as hair loss and bone marrow suppression, and may even cause congestive heart failure in the pediatric population [38]. Carbon quantum dots conjugated with doxorubicin and transferrin were produced in a step-wise process. First, raw carbon dots were synthesized and purified, which was followed by conjugation of transferrin and subsequent conjugation of doxorubicin, utilizing the available surface functional groups [38]. Transferrin was chosen due to the overexpression of the transferrin receptor on the BBB and tumor cells of interest. Successful uptake of these nanoparticles by the pediatric tumor cell line, SJGMB, has been seen in vitro when compared to doxorubicin alone [38].

Bottom-up carbon quantum dots synthesized using L-aspartic acid and D-glucose via pyrolysis have the ability to act as a targeted imaging and diagnostic agent for gliomas when injected intravenously in a mouse model [37]. This is due to the carbon quantum dot's excitation-dependent photoluminescence behavior [37]. It is hypothesized that these carbon quantum dots are transported across the BBB with the assistance of transport proteins, such as GLUT1 and ACST2, using the glucose and aspartic acid ligands [39]. This hypothesis can be supported by the known abundance of these transporters, specifically found on the surface of the BBB and gliomas [40].

7.2.4 Liposomes

Liposomes are spherical vesicles that consist of one or more lipid bilayers, which form an internal aqueous compartment. Liposomes have relatively impermeable

lipophilic outer shells and are often composed of phospholipids. They have been among the most investigated structures for drug delivery in recent history because of their excellent biocompatibility, biodegradability, low toxicity properties and ability to incorporate both hydrophilic and hydrophobic drugs. Liposome-based drug delivery systems are based on the aqueous core, which provides an environment in which therapeutic drugs can be sequestered and have been widely used to improve drug efficacy or to eliminate drug-related toxicity [41].

Adsorptive-mediated transcytosis of liposome-based drug delivery systems utilizes the negatively charged property of endothelial cells. By creating positively charged or "cationized" liposomes, these liposomes are able to target and bind to the BBB, mediating the incorporation of their contents across the BBB. Studies have shown that liposomes conjugated with cationized bovine serum albumin are able to adsorb onto the BBB in in vivo rat models, while liposomes conjugated with naive bovine serum albumin did not achieve similar levels of adsorption [42].

7.2.4.1 Targeted Delivery of Liposomes to CNS

The process of delivery of liposomes to a target is generally complex and non-specific. An approach referred to as "Molecular Trojan Horse" has proven to be effective in delivering molecules through the blood–brain barrier to the brain by exploiting receptor-mediated transcytosis. This method consists of surface-modifying the exterior liposomes to include ligands specific to receptors present on the target of interest. Different ligands have been researched and include peptides, monoclonal antibodies and aptamers. As mentioned above, one common receptor that is present on the surface of the brain capillary endothelium is transferrin receptor (TfR). TfR is responsible for the transport of holo-transferrin from blood to the brain, at the same time as mediating reverse transcytosis of apo-transferrin from the brain to blood [43]. Recognition elements, such as transferrin or antitransferrin receptor antibody, and a transferrin receptor-specific aptamer have been used to effectively and specifically deliver the liposomal payload, such as anticancer drugs, in order to improve the specificity of cellular uptake while lowering overall toxicity [44].

7.2.4.2 Liposomes for Treatment of CNS Infection

One promising CNS application of liposome-mediated drug delivery is based on increasing the bioavailability of antiretroviral pharmaceuticals for the treatment of CNS infection. Generally, loading efficiency of anti-HIV drugs has been reported to be low, while the portion that is successfully loaded suffers from a high amount of leakage. In a study performed by Li and colleagues, liposomes were filled with a zidovudine (AZT) prodrug and zidovudine myristate (AZT-M), in order to avoid leakage, and were subsequently injected intravenously into the rat model. Although

higher concentrations of AZT were found in the brain post-AZT-M liposomal injection when compared to the free AZT injection, the greatest increase of the drug was found in the liver and spleen. This is important for this type of treatment, because drug accumulation in the reticuloendothelial system is favorable, as it improves the therapeutic index of antiretroviral pharmaceuticals [45].

7.2.4.3 Liposomes for Treatment of CNS Neoplasia

One of the shortcomings of many anticancer drugs is that they suffer from a lack of specificity, which ultimately results in cytotoxicity towards not only the tumor cells but also towards the healthy cells. In order to reduce the severe systemic toxic side effects, these anticancer drugs can be incorporated into a targeted payload-carrying system, which will ultimately reduce non-specific toxicity and improve the efficacy of the treatment [46]. Transferrin can once again be used as a target in CNS neoplasia treatments, as it is highly expressed on the surface of tumor cells. For example, antitransferrin receptor antibody RI7217 can be conjugated to the surface of liposomes, which would not only allow for targeted delivery of the payload-carrying liposomes to BBB, resulting in their subsequent fusion and release of the payload, but also for targeting transferrin presented on the surface of tumor cells [47]. One example of the use of liposomal formulation in the treatment of neoplastic meningitis was examined by Dominguez et al., when the liposomes were loaded with cytarabine, a cell-specific antimetabolite that is used to kill tumor cells, while they are in their S-phase of the cell cycle. Cytarabine was encapsulated in the aqueous compartments of the liposomal wall, made up of phospholipids, triglycerides and cholesterol. Therapeutic efficacy of cytarabine is largely dependent on the presence of a large dose of the drug during a specific phase of cell development, which means that the concentration of the drug and the length of treatment must be carefully tailored. Liposomal cytarabine showed sustained release of the drug, helping to maintain the proper concentration, which spanned the cell cycle, allowing specific S-phase targeting [48].

7.2.4.4 Liposomes for Treatment of Ischemic Stroke

Stroke has a worldwide incidence of 15 million new cases each year and a mortality rate of approximately 30% [49]. Ischemic stroke accounts for approximately 80% of all stroke events. Liposome-based therapeutic strategies that are discussed below differ from the ones above as they are specifically targeted to the vasculature of the brain and do not require the penetration of the BBB.

Liposomes prepared from dipalmitoylphosphatidylcholine (DPPC)/dioleoylphosphatidylcholine (DOPC)/cholesterol (Chol) have shown promise in the acute neuroprotection during ischemic stroke. These liposomes allow for a controlled release of nitric oxide (NO), a regulator of cerebral artery tone and a neuroprotector. NO is usually applied to a patient systematically and can be

scavenged by hemoglobin. These liposomes are able to deliver NO specifically to the area of injury and achieve a high local concentration, allowing for increased benefit and neuroprotection [50].

Another group, led by Hwang, was able to create a liposome composed of a mixture of phosphatidylcholine (PC), Chol and phosphatidylethanolamine. This liposome can be used to deliver angiogenic peptides derived from the vascular endothelial growth factor to an ischemic brain in a rat model [51]. This liposome can be administered intra-arterially and is able to target the ischemic hemisphere of the brain. The application of these liposomes resulted in the attenuation of the perfusion defect and increased expression of a gene involved in angiogenesis (angiopoietin-2), with the consequent increase of glucose consumption and vascular density, without promoting inflammation [51].

7.2.4.5 Liposomes for Treatment of Cognitive Deficits

Another payload/targeting liposome system was developed by McConnell and colleagues, where a transferrin-targeting aptamer (TRA) was used to surface-modify a liposome, which was loaded with a dopamine aptamer (DAL). This dual-aptamer system (DAL-TRAM), with one aptamer acting as the mediator and the other as the payload, allowed for specific targeting and take-up of the liposome through the BBB and subsequent safe delivery of the nucleic acid agent. Other advantages of this system include the ability to modify the composition of liposome walls to include fluorescent elements that can be used in real-time imaging of the distribution, and the delivery of a high local concentration of the payload at the target of interest. This particular study confirmed the ability of an acute systemic administration of DAL-TRAM to attenuate hyperlocomotion in cocaine-treated mice. This was achieved by the TRA-driven specific delivery of a dopamine aptamer to the brain [44].

7.2.4.6 Nanoparticle for Improved Neural Axis Imaging

Magnetic resonance imaging (MRI) has revolutionalized the diagnosis and management of CNS disease, and contrast agents (CA) have been heavily used over the past several decades to enhance the diagnostic value of the obtained images. Improving the efficacy of contrast agents can be facilitated by allowing both the optimization of the magnetic properties of the CA and the optimization of the pharmacokinetics and distribution of the CA in the patient. Contrast agents consisting of DNA aptamer-gadolinium(III) conjugates have been shown to provide a single system in which these factors can be addressed simultaneously. We have shown that a 15mer thrombin aptamer could be conjugated to diethylenetriaminepentaacetic (DTPA) dianhydride to form a monoamide derivative of the linear open-chain chelate present in the commonly used contrast agent Magnevist(®) [52]. The stability of the conjugated DNA aptamer-DTPA-Gd(III) chelate in a transmetallation study using Zn(II) was found

to be similar to that reported for DTPA-Gd(III). Relaxivity enhancements of 35 ± 4 and 20 ± 1% were observed in the presence of thrombin compared to a control protein at fields of 9.4 and 1.5 T, respectively.

Multifunctional nanoparticles have also been developed towards applications in noninvasive magnetic resonance imaging and axonal tracing. We have developed multifunctional nano-biomaterial by deliberately combining functions of superparamagnetism, fluorescence and axonal tracing into one material [53]. Superparamagnetic iron oxide nanoparticles were first synthesized and coated with a silica layer to prevent emission quenching through core–dye interactions; a fluorescent molecule, fluorescein isothiocyanate, was doped inside second layer of silica shell to improve photostability and to enable further thiol functionalization. Subsequently, biotinylated dextran amine, a sensitive axonal tracing reagent, was immobilized on the thiol-functionalized nanoparticle surfaces. The resulting nanoparticles were then characterized by transmission electron microscopy, dynamic light scattering, X-ray diffraction, X-ray photoelectron spectroscopy, UV–Vis spectroscopy, magnetic resonance imaging and fluorescence confocal microscopy. In vitro cell experiments using both undifferentiated and differentiated Neuro-2a cells showed that the cells were able to take up the nanoparticles intracellularly and that the nanoparticles showed good biocompatibility. This new material demonstrated promising performances for both optical and magnetic resonance imaging modalities, suggesting its promising potential in applications such as in noninvasive imaging, particularly with respect to neuronal tracing.

7.3 Inorganic Nanoparticles

7.3.1 Gold Nanoparticles

Gold nanoparticles, shown in Fig. 7.8, (<10 nm) have a long-standing history in human use, dating to medieval times when they were used to create decorative glass. Gold nanoparticles possess a “surface plasmon resonance” phenomenon, which is a non-radiative electromagnetic surface wave that propagates in a direction parallel to the negative permittivity/dielectric material interface. This allows for the measuring of the adsorption of the nanoparticle. Ligands can be attached to the nanoparticles during synthesis via a thiol bond or through an exchange reaction after synthesis with thiolated ligands. Gold nanoparticles are also easy to prepare and can undergo versatile surface-modifications while being highly biocompatible. Gold nanoparticles have a number of advantages as both an imaging reagent and a therapeutic delivery system in the CNS [10].

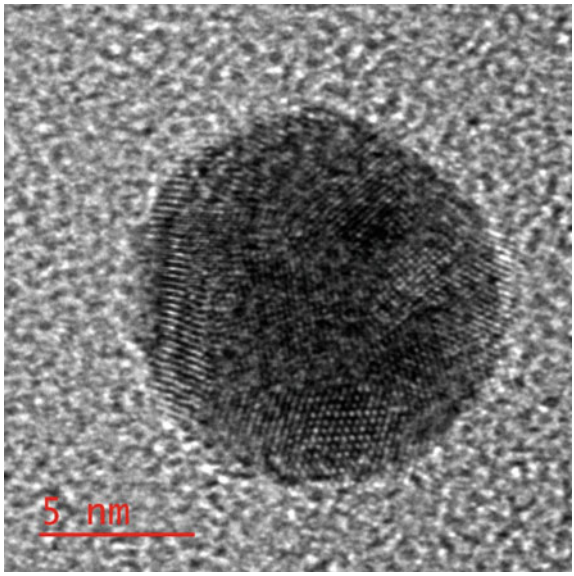

Fig. 7.8 Representative TEM image of a gold nanoparticle

7.3.1.1 Gold Nanoparticles for Diagnoses of CNS Tumors

Currently used as X-ray contrast agents, gold nanoparticles are advantageous over iodine as they are less nephrotoxic and produce higher contrast enhancement [54]. Gold nanoparticles can be used to specifically target tumors and are used in the imaging of kidney carcinomas. However, gold nanoparticles, to date, have shown a low level of accumulation in the brain. Therefore, more is required to realize the potential of gold nanoparticles in relation to diagnostics, especially with respect to CNS tumors [10].

7.3.1.2 Gold Nanoparticles for Treatment of CNS Tumors

Therapeutic agents have been effectively attached to the surface of gold nanoparticles, which allowed them to be transported into cells. Specifically, gold nanoparticles surface-modified with chemotherapeutics, such as paclitaxel and doxorubicin, have been successfully synthesized and tested [55, 56]. Additionally, doxorubicin-coated gold nanoparticles were able to enter tumor cylindroids [56].

7.3.1.3 Gold Nanoparticles for Treatment of Spinal Cord Injury

Gold nanoparticles may also have a role in the treatment of spinal cord injury. In 2016, Zhang et al. created a gold nanoparticle-based carrier surface-modified with wheat germ agglutinin horseradish peroxidase (WGA-HRP), which concurrently acted as

a targeting agent and a visual reporter and either dipropylcyclopentylxanthine or theophylline, drugs that are used as a selective antagonist for adenosine A1 receptor for the treatment of respiratory dysfunctions. WGA-HRP demonstrated the ability to penetrate neurons with adsorptive-mediated endocytosis and to reach neuronal cell bodies by retrograde transport. Although the drug was injected intramuscularly into the diaphragm, in vivo drug release was seen in the cervical spinal cord and medulla nuclei in an experimental rat model [57]. This has potential applications of drug delivery directly targeted into the cervical spinal cord in the context of spinal cord injury.

7.3.1.4 Gold Nanoparticles for Treatment of Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is an aggressive form of malignant glioma. One of the most common adult central nervous system neoplasias, GBM represents nearly 77% of all malignant brain tumors [58]. There are an estimated 25,000 new cases a year in the USA. Current treatments include chemotherapy, radiotherapy and surgical resection [58]. Despite these treatments and advancements in current oncological treatments, the mean survival for GBM patients is only 11 months [59].

Hainfeld et al. were able to create a radiosensitization strategy using gold nanoparticles for brain tumor treatment [54]. Using a mouse model, 1.9-nm-diameter gold nanoparticles injected intravenously were able to preferentially localize into brain gliomas with a 19:1 tumor-to-healthy parenchyma ratio. The relevant accumulation of gold nanoparticles into the tumor tissue enabled a high resolution for tumor imaging by computed tomography and increased sensitivity of the glioma to radiation, prolonging the life the experimental animals when compared to radiation alone [54]. Other studies have explored the use of gold nanoparticles that are surface-modified with polyethylene glycol (PEG) for the treatment of GBM. The BBB can be a hurdle in the clinical treatment of GBM, and in order to circumvent it, PEGylated gold nanoparticles were employed. They were shown to have antibiofouling properties, prolonging systemic circulation half-life and enhancing the efficacy of the treatment. Specifically, these PEGylated gold nanoparticles were tested in conjunction with radiation therapy in cell culture experiments and an animal model. The combination of gold nanoparticles and radiation therapy resulted in localized and specific DNA damage in the GBM tumors [60], demonstrating that gold nanoparticles may not only be useful in carrying chemotherapeutics but can also be used with respect to combination therapy.

7.3.2 Silver Nanoparticles

Silver nanoparticles, shown in Fig. 7.9, (1–100 nm) are similar to gold nanoparticles in the respect that they can also theoretically carry various payloads to specific targets with the assistance of the appropriate surface-modification. Ultra-fine silver

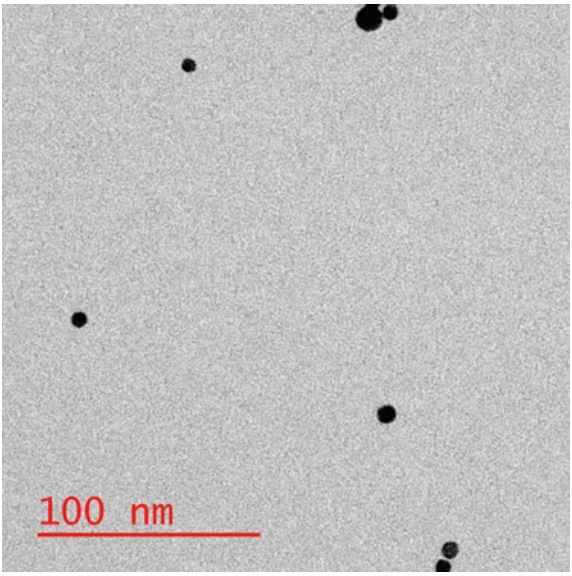

Fig. 7.9 Scanning electron microscopy image of silver nanoparticles 20 nm in size

nanoparticles can be inhaled and traverse the blood–lung barrier to move to the circulatory system [61]. However, it has been reported that silver nanoparticles may interact with cerebral microvasculature to produce a proinflammatory cascade and induce the BBB inflammation, astrocyte swelling and neuronal degeneration [62]. The mechanism of this reaction remains to be clarified.

7.3.3 Iron Oxide Nanoparticles

When looking at the overall range of inorganic nanoparticles that have been developed, iron oxide nanoparticles are among the most widely researched. In fact, ferumoxytol, the first iron oxide conjugate, has been approved for limited clinical use by the FDA [63, 64]. Specifically, ultra-small iron oxide nanoparticles are applicable in imaging procedures and utilize their superparamagnetic properties to increase the signal intensity of T1-weighted images and decrease signal intensity of T2*-weighted images in magnetic resonance imaging (MRI) [64]. These properties thereby allow for iron oxide nanoparticles to be used as effective contrast media in neuroimaging platforms [63]. Since iron oxide can be toxic within the biological system, these superparamagnetic nanoparticles have been coated with biocompatible polymers, such as dextran or polyglucose sorbitol carboxymethyl ether, which concurrently allows them to permeate the BBB. One example of such imaging involves intravenous administration of ferumoxytol for the purpose of imaging malignant brain tumors. When compared to conventional gadolinium-based contrast media, ferumoxytol demonstrated higher signal resolution of brain tumor lesions [65, 66].

Other studies have shown effective contrast enhancement with the use of transferrin-conjugated superparamagnetic iron oxide nanoparticles for brain glioma detection [67]. A plethora of other studies include applications in imaging of neuroinflammation and stroke diagnosis. It is obvious that the use of iron oxide nanoparticles presents a promising novel avenue for the diagnosis of a wide variety of CNS disorders.

7.3.3.1 Iron Oxide Nanoparticles in Combination Therapy

Recently, much focus has been directed towards developing nano-agents that can be used for their combined ability to act as imaging and therapeutic agents. One such example was developed by Hu et al., producing a porous iron oxide nanoparticle, loaded with doxorubicin [68]. The porous iron oxide nanoparticles (PIONs) were used as an imaging contrast agent, utilizing the superparamagnetic properties described above. Contrast enhancement was similar to that achieved by the currently used gadolinium agents. Simultaneously, PIONs were used as a photothermal therapy agent. Near-infrared irradiation was utilized after the PIONs were combined with cancer cells, and their ability to convert near-infrared light to heat was assessed. A synergistic effect was achieved when doxorubicin was slowly released through the disrupted walls of the PIONs, which was the result of the overall temperature increase. When comparing the individual effect of the photothermal therapy or doxorubicin to the synergistic effect of the DOX-PIONs, it was evident that the latter formulation was much more effective as a treatment towards these cancer cells [68]. This study demonstrates that nanoparticles can be used to not only carry therapeutic agents as a surface-modification but in combination therapy as hollow and porous carriers, with the carrier shell having its own purpose in the treatment. This combination of properties allows the achievement of an impressive synergistic effect and can increase the effectiveness of the treatment.

7.4 Concluding Remarks

There are many promising pharmaceuticals that can help in the diagnosis and treatment of CNS diseases. However, the BBB presents a physical barrier which limits the use of these therapeutics. Only small, lipophilic drugs can pass through the BBB. This excludes the use of 100% of the large molecule and 98% of small molecule therapeutics [69]. To circumvent this barrier, a variety of physical, chemical, and biological methods of BBB disruption have been employed. However, these methods are far from ideal and cause permanent damage to the BBB with devastating consequences. Nanoparticle-based drug delivery systems present a noninvasive method of drug delivery into the CNS. Nanoparticles are able to carry both lipophilic and lipophobic drugs by entrapping the drugs into cavities, adsorption or conjugation. Nanoparticles are also highly customizable with regard to size, charge and surface functional groups. These advantages should allow for the specific targeting of diseased cells,

combination therapy with more than one drug and controlled and sustained release in the CNS. In conclusion, current literature shows that there have been significant advances in the research of nanoparticles for the next generation of CNS pharmaceuticals.

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