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Mini Review Article

Nanocarriers for Successful Drug Delivery Across Blood-Brain Barrier

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Abstract

The blood-brain barrier (BBB) is known as a highly selective semipermeable barrier between neural tissue and bloodstream. The protective feature of the BBB has a key role in maintaining ion and molecule exchange. The neurodegenerative diseases such as multiple sclerosis, brain tumors, stroke, Parkinson's, and Alzheimer's diseases can lead to BBB dysfunction. However, in a damaged BBB, drug delivery into the brain is still a big challenge. Nanoparticulate drug delivery systems are able to encapsulate drug molecules and mediate drug penetration through the BBB in neuronal pathologies by targeting specific transport processes in the brain vasculature. In this mini review, we will highlight nanoparticulate delivery systems used to deliver therapeutic agents trough the BBB as well as the factors affecting their transportation following systemic administration.

Keywords: *Central nervous system, Brain, Blood brain barrier, Nanoparticle, Drug delivery.*

Introduction

The blood-brain barrier (BBB) is a unique anatomic structure at the interface between the central and peripheral nervous systems that is mainly constructed by tight junctions (TJ) and adherens junctions (AJ) [1]. The BBB becomes hyper-permeable to macromolecules during some brain pathologies such as brain tumors, stroke, Parkinson's disease (PD), and Alzheimer's disease (AD), resulting in a range of inflammatory responses and neuronal injuries [2]. However, the majority of currently available therapies are unable to reduce the main symptoms and improve the quality of life. Until now the research for effective treatments shows no significant improvement and drug delivery is a huge challenge that must be overcome. Among various strategies developed to overcome the BBB, a high attention has been centered for the fabrication of nanoscale drug carriers. Nanoparticles (NPs) are suggested as one of the most versatile platforms which can be regarded as the future of brain drug delivery. NPs possess the capacity to protect the loaded cargo while effectively transporting them into the targeted regions [3]. A wide variety of nanocarriers, such as polysaccharide, lipid, protein, polymeric, and inorganic NPs have been suggested to achieve neurological therapeutics with desired targeted and sustained release properties, mainly when their surface are modified with ligands or surfactants (Figure 1)[4] .

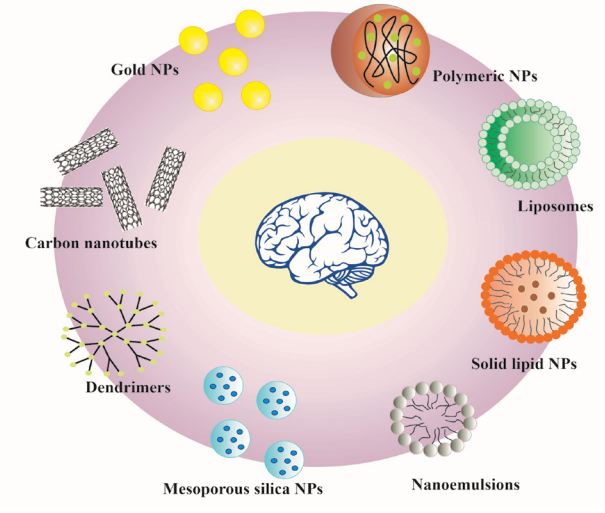

Figure 1. Various nanocarriers reported for treatment of neurodegenerative diseases.

With this in mind, it is an important step to obtain a clear understanding of the BBB damage in pathology due to take benefit of these systems to design novel and versatile NPs capable of specifically targeting injured regions of the brain.

General Concept of the BBB

The central nervous system (CNS) consists from a set of barriers with diverse degrees of permeability due to protect itself from the environmental pathogens including the BBB, blood-cerebrospinal fluid barrier, blood-spinal cord barrier, and blood-retinal barrier [5, 6] . The BBB is known as the most exclusive and extensive barrier which is constituted by a tightly connected layer of the brain endothelial cells and a discontinuous layer of pericytes. The unique characteristics of cerebral endothelium allow it to preserve the functional integrity of the BBB and transendothelial passage of cells [7] More importantly, the endothelial cells express a set of specific proteins, namely TJ and AJ, due to improve the cohesiveness of the barrier [8]. TJs are complex membrane structures composed of transmembrane and cytoplasmic proteins like junctional adhesion molecules, occludin, zonula occludens, claudins, and accessory proteins. Although endothelial cells are tightly connected by a strong cohesive system, the BBB permits the passage of specific molecules and cells into the brain [9]. Paracellular route is referred as the passage between endothelial cells and is used by ions and solutes along a concentration gradient. The mechanism of passage across the endothelial cells is called transcellular [10]. In most cases, the transcellular passage basically takes place by the passive diffusion of hydrophobic substances across the receptors which are specific and selective to the exchange molecules [11]. Hydrophilic molecules (like proteins and peptides), enter the brain by specific transferrin receptors, or depend on a specific transporter, like glucose transporter-1 [12]. Other forms of transport at the cellular membrane occurs via caveolae invaginations. These structures can form carrier vesicles around the substance participating in movement into the brain [13]. Transcytosis pathways through the endothelial cells are being suggested as a mechanism to transport pharmaceutical agents into the brain. ATP-binding cassette transporters restrict the passage of a number of drugs into the brain [14]. A deeper understanding regarding the detailed structure of the BBB will foster the development of novel nanovehicles for the effective delivery of therapeutic molecules which cannot cross the BBB in normal conditions.

NPs for Drug Delivery into the Brain

Neurodegenerative diseases are an increasing public health problem. Nevertheless, only a small number of brain-related drugs (3-5%) have entered the market since most of them were unable to reach the brain tissue in vivo [15]. Therefore, the development of new strategies for the treatment of human neurodegenerative damages is one of the most important challenges facing pharmaceutical companies. The use of nanotechnology for the management of disease referred as nanomedicine is a dominant research field of the 21st century, which exhibits the potential to improve individual and collective health care [16, 17]. Nanomedicine is considered as a combination of technology which include chemistry, physics, engineering, biology, and biotechnology [18, 19]. The recent efforts in the field of nanomedicine have led to a steep increase in the use of nanocarriers due to improve drug passage across the BBB [20-22]. NPs are colloidal particles (1-1000 nm) which can deliver pharmaceutical compounds by encapsulating, physical adsorbing, or covalent bonding [23, 24]. The main requirements for designing novel nanotechnology-based systems to the brain delivery of drugs are the ability of nanosystems to escape from the body,s protective mechanisms such as opsonization and reticuloendothelial system (RES) clearance and the targeted delivery of cargo with penetration across the BBB and endocytosis into the brain tissue [25]. NPs can be fabricated from the natural materials including polysaccharides (e.g. chitosan, alginate, pectin, hyaluronic acid), lipids (e.g. triglycerides, fatty acids, waxes), proteins (e.g. silk, gelatin, albumin), from synthetic polymers (e.g. poly(lactic acid) (PLA), poly (amidoamine) dendrimers (PAMAM), poly (lactic-co-glycolic acid) (PLGA)), and from inorganic materials (e.g. carbon, gold, silicon dioxide (silica)). Although natural nanocarriers can have drawbacks, such as limited tracking feature by imaging techniques, poor capacity for controlled modification, and higher batch-to-batch variability, they show the benefits of providing biological signals to interact with the transporters/receptors expressed on the surface of endothelial cells. Polysaccharides are substrates for receptors present at the cell membrane, mediating the development of targeted nanoscale delivery systems. Polysaccharides can be further classified into the positive (e.g. chitosan) or negative (e.g. alginate, hyaluronic acid, pectin) polysaccharides [26]. The abundant hydroxyl groups of polysaccharide-based NPs allow them to interact with the biological tissues via noncovalent bonds. Among the polysaccharide-based nanocarriers extensively investigated for brain drug delivery is chitosan nanocarriers [27]. The free amino groups of chitosan confer an overall cationic charge at physiological pH, providing an important advantage to avoid opsonization and interact with the negatively charged epithelial cells. More importantly, chitosan nanocarries can open the cellular TJs in a reversible and transient manner [28]. For example, chitosan nanocarriers have been reported to improve the brain targeting via the interaction with the BBB endothelial cells and also cerebral capillaries, after intravenous administration, even with an intact BBB [29]. Hyaluronic acid has widely been investigated in the preparation of drug-polymer conjugates for brain targeted drug delivery, as it can be easily conjugated and functionalized with chemotherapeutic drugs [30]. The cellular uptake of hyaluronic acid-drug conjugates is mediated by the CD44 receptors. Hyaluronic acid-paclitaxel conjugates were exhibited to decrease p-glycoprotein efflux of drug [31]. Liposomes are small lipid-based nanovesicles consisted from concentric phospholipid bilayers. Regarding PD, Wu et al. [32] described liposomes as a possible valuable system to improve the brain bioavailability of the growth factor when administered intravenously in rats. In another study, resveratrol has been loaded in the liposomes to improve its bioavailability and antioxidant activity in an animal model of PD [33]. Another avenue of brain targeting is the use of lipid nanocarriers which are composed from fatty acids as well as mono-, di-, and tryglycerides. Nanostructured lipid carriers (NLC) and solid lipid NPs (SLNs) are the most commonly applied lipid nanosparticulate systems. Such lipid matrices are able to enhance the drug colloidal stability, as well as bypass the BBB because of their

hydrophobic precursors, and without worrying about the toxicity of the degradation compounds [34]. More importantly, they provide enhanced mechanical stability, remain in solid state at body temperature, and exhibit a controlled drug release. However, the amount of drug loaded in NLCs was demonstrated to be higher in comparison to SLNs which could be attributed to their imperfect crystal structure [35]. Human serum albumin NPs have attracted much research attention in brain drug delivery because of their large loading capacity and the fact that they are physiologically well tolerated when administered intravenously. In a recent research, andrographolide-loaded human albumin NPs were able to penetrate in both undamaged and damaged brain tissues. In vivo data exhibited that albumin NPs injected to TgCRND8 mice, an AD animal model were well tolerated [36]. Similarly, Bergonzi and co-workers [37] investigated that albumin NPs can accumulate in different regions of brain tissue and did not induce inflammatory effects. PLA, and PLGA are FDA-approved synthetic polymers which have been widely investigated for drug delivery into the brain in the past years because of their sustained release properties. Moreover, these polymers can be degraded inside the body with no immune or other adverse reactions [38]. Song et al. [39] developed PLA NPs for efficient brain drug delivery. These particles exhibited low toxic effect and high cellular uptake. In another work, Sanches-Lopez et al. [40] fabricated PLGA NPs for the transport of memantine in AD. The authors demonstrated that the NPs are safe for brain cells and could penetrate through the BBB. PAMAM dendrimers are considered as one of the smallest nanosystems available today, that have excellent efficacy to improve the CNS disorder treatment. The generation, size, and surface charge of dendrimers can be tuned to achieve a wide number of nanovehicles for drug delivery to brain cells in vivo [41]. Several inorganic nanocarriers were suggested for their potential to penetrate across the BBB. Inorganic NPs have superior benefits over polymeric NPs to control their shape, size, simplicity of preparation, and functionalization. Notably, inorganic NPs can be easily detected and tracked by analytic techniques like ICP-MS or microscopy techniques like magnetic resonance imaging [42]. However, inorganic NPs are also associated with some drawbacks as they might not be removed via the kidneys or exhibit undesirable toxic effect (e.g. fullerenes and carbon nanotubes may form oxygen radical and cause lipid peroxidation) [43, 44]. The physicochemical characteristics of NPs significantly determine the major mechanisms of transport through the BBB. Some of the passage processes of NPs have been illustrated in the Figure 2:(i) NPs are capable of opening TJs or causing transient toxicity which allows the transport of loaded cargo [45]; (ii) NPs undergo endocytosis by endothelial cells, their cargo is entered into the cytoplasm and finally is directed into the endothelium abluminal side [46]; (iii) NPs are entered into endothelial cells via transcytosis [47]; or (iv) by using a combination of different transport mechanisms mentioned previously. Receptor-mediated transcytosis is a principal pathway that NPs target specific receptors expressed on the BBB like transferrin receptors [48] and low-density lipoprotein receptors [25, 49]. Targeted drug delivery is often achieved using different targeting moieties like peptides [50], proteins [51], and

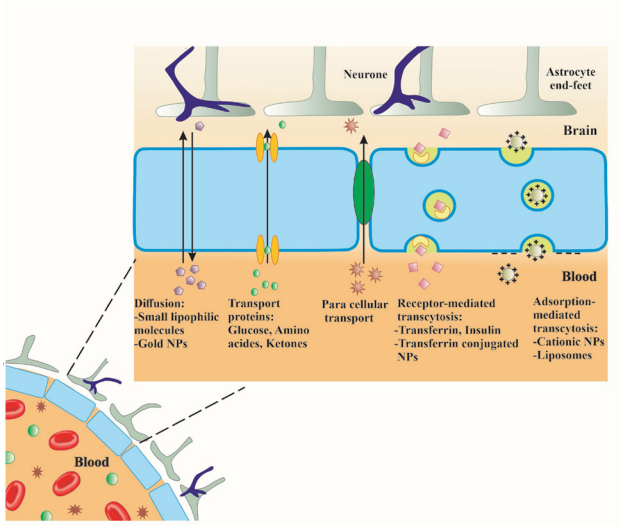

Figure 2. Strategies for NPs to cross the blood-brain barrier.

antibodies [52] chemically or physically immobilized on the NPs surface.

NPs could potentially offer an exciting strategy for the treatment of brain pathologies via modulating size, shape, charge, and surface chemistry. Control over these characteristics can in fact lead to the improvement of the NPs stability in the blood stream, avoid RES clearance, enhance drug penetration across the BBB, and allow to release their payloads only at the target site [23, 53].

Factors Affecting the Passage of NPs Across the BBB

During the last decade, NPs have attracted considerable interest as promising platforms for enhancing brain drug delivery. Nevertheless, it is very difficult to determine definite design principles through the resulting data because of differences in shape, size, charge, and surface chemistry of NPs. It is believed that these factors can affect the systemic circulation, cellular uptake, and BBB passage of NPs in vivo. Several studies reported that the size of NPs exhibits a critical impact in their essential physiological functions. Notably, there is a clear inverse relationship between particle size and efficiency to penetrate the BBB [54, 55]. Therefore, the NPs size should be carefully controlled as particles with size more than 100 nm are unlikely to penetrate into the brain tissue. For example, in several animal models of stroke, AD or PD, the average penetrated NPs size was obtained to be 50-100 nm. Shilo et al. [56] also reported that the size of around 70 nm is optimal for the cellular uptake of gold NPs. Another key parameter controlling the brain distribution of NPs is shape [57]. NPs can be engineered into different shapes such as sphere, cubic, triangle, and rod-like. Since spherical NPs are relatively easy and simple to develop, a large number of studies in the field of NPs have been carried out using spherical NPs. In in vitro studies, the antibody-coated nanorods displayed larger adhesion propensity compared with their spherical counterparts. Rod-shaped polystyrene NPs modified with the specific anti-transferrin receptor antibodies demonstrated a increase in particle brain uptake in vivo in comparison to the spherical particles that carried the same

antibody [58]. The surface charge on NPs is commonly defined as the zeta potential. It is a principal parameter that influences the passage of NPs across the BBB. NPs with a high positive zeta potential were reported to cause immediate toxic effects on the BBB [59]. Therefore, a large number of researches has been focused on the moderately (between -1 to -15 mV) [47, 60] or highly (between -15 to -45 mV) [61] negative NPs. However, several positively-charged NPs with moderate (up to 15 mV) or high (above 15 mV) values of zeta potential were demonstrated to be able to penetrate efficiently into the brain [45, 62]. In recent years, different types of ligands have been applied to assist NPs to penetrate through the BBB: (i) targeting ligands that bind directly to receptors and/or transporters at the BBB [63]; (ii) ligands that mediate the nanocarriers interactions with the BBB receptors and/or transporters following the adsorption of specific proteins in the bloodstream [64]; (iii) ligands that aim to an increase of the charge and hydrophobicity of particles [65], and (iv) ligands that reduce protein adsorption and improve blood circulation time [66]. In the first case, the surfactants can act as an anchor for apolipoproteins, enhancing BBB permeability through the recognition of lipoprotein receptors which are highly expressed on the brain endothelium. For example, coating with tween 80 facilitates apolipoprotein E and/or A-I adsorption onto the nanocarriers surface. In the second case, different receptors like transferrin receptor [67], insulin receptor [68], and glucose transporter [69] can successfully be used for targeted brain drug delivery. In the third case, amphiphilic peptides are capable of facilitating NPs uptake by BBB endothelial cells. With this aim, doxorubicin-loaded liposomes were functionalized with cell-penetrating peptide R8 conjugated with oleic acid. Here, the brain distribution of doxorubicin by R8-conjugated oleic acid-modified liposomes was higher than that of unmodified liposomes [70]. In another investigation, carbon nanotubes modified by amine groups were developed to efficiently penetrate across the BBB via transcytosis process [71]. Notably, the passage of nanocarriers across the BBB is strongly affected by the number of ligands as well as their interaction with the receptors. The characterization of how ligand density affects nanocarrier transport across the BBB remains an active area of investigation. The results supported the known fact that NPs conjugated with ligands at a low density (low avidity) show the highest affinity to interact with the BBB receptors. The density of ligands for cell surface targeting depends both on the ligand size and NPs surface area. A greater degree of avidity and selectivity can be obtained using NP systems conjugated with multiple targeting ligands [72]. The NPs avidity should be controlled for efficient brain drug delivery. Too high avidity will limit NPs to be penetrated into the brain parenchyma. For instance, gold NPs attached with a large number of transferrin (100-200 molecules) remain strongly bound to the endothelial cells whereas those with less transferrin (20-30 molecules) can efficiently bind to the receptor and be transported into the brain [47]. NPs dispersed in a physiological environment adsorb plasma proteins, causing the formation of the protein corona [73]. For example, it has been found that different types of serum proteins (over 70 proteins) adsorb onto the gold NPs [15]. The formation of protein corona may change the surface chemistry and aggregation state of NPs. Moreover, protein corona results in the rapid clearance of NPs from the blood stream by the liver and spleen after recognition by the RES [74]. Therefore, the availability of NPs is decreased for the accumulation in the brain. The surface charge of NPs exhibits a critical effect in their clearance. Arvizo and co-workers [75] reported that neutral and zwitterionic NPs demonstrated a prolonged blood circulation times than positive and negative NPs after intravenous administration. The most common method to prevent protein corona formation while maintaining the safety and efficacy is to use molecules with corona anti-fouling capability. The use of polyethylene glycol (PEG) offers anti-fouling properties to the NPs surface. PEG-coated NPs exhibit minimal surface charge, causing lower NPs opsonization, and avoiding uptake by the RES [76]. It was reported that the grafting of NPs with PEG chains (5kDa) is effective at decreasing protein adsorption and slowing the clearance of particles from the blood stream [15]. Therefore, PEGylation of NPs provides more effective accumulation of NPs in the brain tissue [77]. In another recent study, 78 nm PEG-coated PLGA NPs showed better diffusion into the brain tissue compared with the uncoated NPs. Similarly, PEGylated NPs with near neutral surface charge and size of 115 nm were able to effectively spread by diffusion within the brain parenchyma, following systemic injection [78]. In summary, NPs penetration through the BBB is influenced by several parameters at different extents. Therefore, nanotechnology-based BBB crossing strategies require nanocarriers that pass more effectively across the BBB but also carriers that are slowly eliminated from the systemic circulation.

Future Prospects

The BBB plays a key role in the proper maintenance of CNS integrity. The pathological disruption of the BBB is associated with different neurological diseases. Therefore, future studies are needed to determine the mechanisms underlying the BBB regulation in the healthy and damaged brain. Although it remains unclear exactly whether dysfunction of CNS maintenance signals or breakdown signals from the pathological state leads to the BBB dysfunction, we now have accumulated extensive knowledge about physical and molecular alterations in the pathological disruption of BBB. Nanocarriers are small colloidal particles which have an increasingly growing potential to protect drugs, enhance their circulation time, and provide a controlled release of the drug payload, after intravenous administration. In recent decades, some methods have been investigated to improve the passage of nanocarriers through the BBB. The physicochemical features of nanocarriers such as size, shape, charge, and ligand density have important effects in the transport of particles through the BBB. Moreover, researchers have started to display some of antibodies, coating ligands, and other directing agents to efficiently deliver nanocarriers to the brain. A wide variety of researches have been conducted to report the restorative impact of nanocarriers on animal models of neurological diseases such as AD, PD, and stroke. Nevertheless, it is critical to bear in mind that an experimental model cannot mimic fully a given human disease. Therefore, more studies are needed to explain the differences and similarities of nanocarriers passage in healthy and disease animal models. The safety and efficacy of

nanocarriers fabricated in pre-clinical tests has to be carefully evaluated in future clinical trials. Nanocarriers are significantly accumulated in other body organs like spleen, kidney, and liver. For this, it is important to develop nanoformulations that release the drug in a controlled or triggered manner only after the drug-loaded nanocarriers enter the brain. The clinical translation in the area of regenerative medicine will be facilitated by the future developments in novel triggerable nanocarriers. Another main area that needs further research is the development of nanocarriers with the ability to target specific type of brain cells. In summary, the main alterations occurring in neurological disorders can be used to design more efficient brain-directed nanoplatforms containing pharmaceutical agents which are able to reach the clinic.

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Conflicts of Interest

The authors declare no conflicts of interest.

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