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A Review on Novel Techniques for Drug Delivery to the Brain

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ABSTRACT

Drug delivery to brain is still a challenging task due to the presence of the blood–brain barrier (BBB), a very restrictive barrier mainly composed of tightly sealed endothelial cells. The anatomy and physiology of BBB strictly regulates the brain access and clearance of endogenous and exogenous molecules from the systemic circulation. It is estimated that more than 98% of the new discovered central nervous system (CNS) potential drugs does not cross the BBB, failing to achieve therapeutic concentration within the brain parenchyma. Recent developments in the field of molecular biology enabled scientists to better understand the BBB and thus delivery of drugs to the brain, particularly under different pathological conditions. The aims of this Review are to outline current research in the field of brain barriers, the main advances made since 2000, the barriers to progress, and to recommend research priorities and the resources needed to advance the field. Applications of nanotechnology in drug transport, receptor-mediated targeting and transport, and finally cell-mediated drug transport will be discuss in the review. The challenge of delivering an effective dose of drug to the brain is formidable; solutions will likely involve multiple strategies that take into account the novel drug delivery systems as well as BBB biology.

Keywords: Blood–brain barrier, Drug delivery, Nanoparticles, Liposomes.

1. INTRODUCTION

The brain is a unique organ highly protected from the periphery by two major barriers, the blood–brain barrier (BBB) which displays the largest surface area and the blood–cerebrospinal fluid barrier (BCSFB). The BBB presents a wide permeability range, highly regulates intracellular and intercellular signaling pathways and overall maintains CNS homeostasis [1]. The BBB is a dynamic barrier protecting the brain against invading organisms and unwanted substances. It is also the most important barrier impeding drug transport into the brain via the blood circulation [2]. It is now well accepted that the functional unit of the BBB includes more than just capillary endothelial cells (Figure 1). Several other cell types, in particular pericytes and perivascular astrocytes are in constant and intimate contact with the endothelium and maintenance of the brain capillary phenotype seems to be critically dependent on interactions with these other cells [3-5]. Still many brain or central nervous system (CNS) associated diseases remained untreated by effective therapies due to the inability of many therapeutic molecules to cross the BBB, BCSFB, or other specialised CNS barriers to reach the specific areas of brain [1].

The restricted and highly controlled access to the brain can be summarized as a combination of following factors:

1) Tight junctions which are sealing the intercellular gap

2) Reduced rate of pinocytosis from the luminal side which prevents uncontrolled cell entrance
3) No fenestration which blocks the intercellular passage of the endothelium
4) An enzymatic barrier which presents the second line protection against unintentionally entered molecules, proteins or viruses
5) An efflux transporter system such as P-glycoproteins and others which removes small molecules from the endothelial cells before they reach the abluminal or basal side

In the absence of an effective BBB drug delivery technology, the brain drug developers are left with the traditional ineffective brain drug delivery strategies, including transcranial drug delivery to the brain, BBB disruption, or small molecules. Transcranial drug delivery, such as convection-enhanced diffusion, only delivers drug to the local injection site [6] and is ineffective as a brain drug delivery technology for the 1200g human brain. BBB disruption leads to chronic neuropathologic changes [7] and is too toxic to be widely used in humans. Small molecules are hardly an alternative strategy because 98% of small molecules tested do not cross the BBB. To be brain penetrating, the small molecule must be lipid soluble, form <8–10 hydrogen bonds with water, and have a molecular weight <400–500Daltons [8]. Few small molecule pharmaceutical candidates have these molecular properties. Moreover, even after successful endothelial cell absorption, active efflux mechanisms (ATP-binding cassette transporter) may pump these molecules back into the blood stream [9]. Thus, even if a peptide-mimetic small molecule were produced in lieu of drug development of a recombinant protein, the small molecule would most likely still need a BBB drug targeting technology to advance in clinical drug development.

As many attempts to transport drugs across the BBB could be against the natural function of the BBB, effective approaches or methods should be cautiously assessed with regards to their impact on the overall protective function of BBB. Along with increased knowledge in the field of molecular cell biology, scientists are now aware of receptor expression at the BBB which helps in the advancement of medical technology, and breakthroughs in nanotechnology-based approaches. Thus the present review will explore molecular and biological opportunities at the BBB for transport of therapeutic molecules across BBB under physiologic and pathological conditions, along with the use of modern approaches like ligand-conjugation and nanotechnology to target the BBB via adsorptive or receptor-mediated transport of drug molecules into the brain.

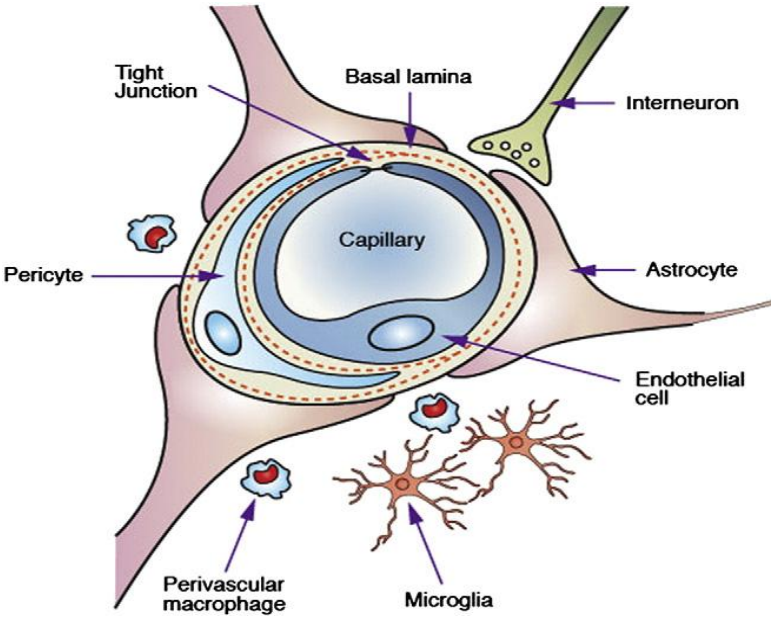

Figure 1. Diagram of blood–brain barrier (BBB) and other components of a brain.

2. VARIOUS ROUTES TO CROSS BRAIN BARRIERS

There are several transport mechanism in brain from where solute molecules can move across the BBB [11,12]. Diffusion of small molecules into the brain can be drive by paracellular and transcellular mechanism. Small water-soluble molecules can simply diffused at a lesser extent while small lipid soluble substances like alcohol and steroid hormones penetrate transcellularly. The essential nutrients required for brain functioning, such as glucose and amino acids are transported by specific receptor-mediated mechanism across BBB.

A better route for selective uptake of biomolecules is Receptor-mediated transcytosis (RMT). Endothelial cells present at BBB, have receptor for the uptake of specific types of ligands, growth factors, enzymes and plasma proteins [12] such as transferring receptor (TfR), insulin receptor, lipoprotein receptors, diphtheria toxin receptor and glutathione transporter. Cellular transcytosis is a more recently identified route of drug transport across the BBB [13], which is one of the well established mechanism for some pathogens such as Cryptococcus neoformans and HIV entry into the brain [14,15]. Immune cells such as monocytes or macrophages are basically involved in such transport route to cross the intact BBB. Cell-mediated transcytosis is unique transport mechanism which is able to help in crossing virtually any type of molecules or materials as well as particulate carrier systems [16].

Pinocytosis by brain cells provides a different route of BBB crossing known as "Adsorption-mediated transcytosis (AMT)" which is triggered by an electrostatic interaction between a positively charged substance, like peptide, and the negatively charged plasma membrane surface (i.e. heparin sulphate proteoglycans). However AMT has a lower affinity but higher capacity than RMT, the development of many new drug delivery systems are focuses on AMT [17].

3. RECENT DEVELOPMENTS IN TRANSPORTING DRUGS ACROSS BRAIN BARRIERS

The rapid advancement and progress in molecular biology has pushed the development of novel drug delivery systems that take advantage of our better understanding of the BBB, the brain and various brain disorders. There is an increase in multi-discipline approaches combing biology, nanotechnology and even biophysics to achieve the common goal. The combination of endogenous transport systems present in the BBB and macromolecular conjugates or surface enhanced nanoparticulate delivery systems such as liposomes, nanoparticles and super molecular complexes has been utilised to access the brain [18]. As discussed previously, transporter proteins, specific receptors or adsorptive endocytosis can be used to realize drug delivery. The characteristics of these systems are

1. Drug may either chemically modified, for instance or conjugated to a ligand so as to facilitate the uptake of drug by the BBB
2. Drug may encapsulate in a surface modified drug delivery system, such as liposomes, nanoparticles or niosomes. The surface of the drug delivery system is often modified with ligands and a hydrophilic polymer such as PEG to prolong the circulation time of the delivery system BBB [19]
3. The homing device and drug delivery system should be non-immunogenic and capable of interacting with receptors presented at the BBB to facilitate the uptake of the drug by the BBB
4. The homing device must be receptor specific, thereby reducing potential side-effects and increasing transport efficiency
5. All systems must have controlled size, therefore their properties are uniform and consistent and their biological fate can be controlled.

The best system will be the one which can fulfill all these characteristics and have a homing device that is specific for a target which is induced or up-regulated by the pathological conditions.

Recent advances in nanotechnology have created exciting opportunities to fulfill above requirements for the management of brain diseases and disorders [20-22]. Nanocarriers are an emerging class of drug delivery systems that can be easily tailored to delivery drugs to various parts of the body, including the brain. In the past decade, it has been attracting increasing attention for its use in transport of drug across the BBB due to the rapid increase in our understanding of receptors and the fast development in polymer chemistry and nanotechnology. Besides being nontoxic, biodegradable and biocompatible, nanocarriers are unique because of their size (less than 100 nm) and easily tailored structures due to the material used. They can behave like macromolecules in certain circumstances but they can carry much more drug payload and are capable of controlling drug release. They can carry a range of drugs and their surface properties can be modified for being non-immunogenic [23,24]. These properties make nanocarriers an attractive alternative for transporting drug across the BBB.

Now days, a drug poorly absorbed and distributed to the brain can be encapsulated into a nanocarrier system which interacts well with the endothelial cells at the BBB and produces higher drug concentrations in brain parenchyma. The nanocarriers for brain delivery may further be modified with targeting moieties such as ligand to bind preferentially to a putative receptors or transporters expressed at the BBB for enhanced brain selectivity and permeability. In addition to this, nanocarriers can be further exploited for efficient "drug trafficking" across the barrier structure through membrane transcytosis processes. However, currently no single "ideal" nanocarrier is available for the purpose of drug delivery to brain; still a better pharmacokinetics, improved efficacy and safety have been achieved using these nanocarriers.

3.1 Nanoparticles

Nanoparticles are colloidal systems with compact structure where the therapeutic agent is either entrapped within the colloid matrix or coated on the particle surface by conjugation or adsorption. Because of their compact nature, many nanoparticles can provide sustained, controlled drug release. Nanoparticles are mostly made of polymers, lipids or a combination of both [25-28]. Nanoparticles made of acrylic polymers, especially poly(butyl cyanoacrylate) (PBCA), have been extensively studied for brain drug delivery [27,28]. The very rapid in vivo degradation of PBCA could minimize toxicity due to polymer accumulation in the CNS. Nanoparticle systems made of polylactide (PLA) and poly(lactide-co-glycolide) (PLGA) have also been studied for brain drug delivery. Several-fold increases in the brain level of dexamethasone and vasoactive intestinal peptide were detected when these therapeutic agents were delivered by PLGA and PLA, respectively [29].

PEGlyated polyester nanoparticles have also been studied.

Significantly higher nimodipine concentrations in blood, cerebrospinal fluid and brain tissues were measured in rat models when the drug was delivered by these nanoparticles [30]. Improved brain accumulation of several compounds, especially anticancer drugs, was demonstrated when these drugs were delivered using solid lipid nanoparticles (SLN), lipid nanocapsules or their PEGlyated forms [31]. This could be achieved by administering the SLN orally [32,33], intravenously [31,34,35] and/or transdermally [36,37]. These nanocarriers also provide superior therapeutic effects. The encapsulation efficiency of SLN for hydrophilic compounds can be improved by including an amphiphilic polymer to the lipids to form complexes with the charged, water-soluble drug molecules (Figure 2 B). This modified SLN are sometimes known as polymer-lipid hybrid nanoparticles [38–40].

3.2 Liposomes

Liposomes are small vesicles of unilamellar or multilamellar phopholipid/ lipid bilayers surrounding central aqueous compartments [41]. They are the most studied and clinically recognized nanocarriers owing to their long track record, low toxicity and ability to deliver both hydrophilic and lipophilic compounds reasonably well [42]. Consequently, brain delivery of diverse drugs, including antifungals, chemotherapeutic compounds, anti-retrovirals, anti-epilepsy drugs and anti-ischemia drugs by liposomal formulations has been studied [43,44]. Liposomes for brain delivery can be easily of modified on surface so as to prepare advanced liposomal formulations such as immunoliposomes for targeted delivery [41]. Limitations of fast systemic elimination, quick metabolic degradation and stability issue of liposomes after extended storage, can be improve by surface coating with PEG known as PEGlyation, and thus the circulation time of liposomes can be extended to days [45,46]. Liposomes of the newer generation are also more stable typically have shelf-lives of several months [41] (Figure 2 A).

3.3 Micelles

Micelles are basically spherical aggregates of amphiphilic molecules dispersing in water with their hydrophilic head groups on the surface of the sphere, and their hydrophobic tails collected inside.[47]. A poorly water-soluble, lipophilic compound can be solubilized in the micelle core region for easy administration. An important property of micelles is their ability to increase the solubility and bioavailability of poorly soluble pharmaceuticals. The amphiphilic molecules in micelles are in constant exchange with those in the bulk solution. On the other hand, polymeric micelles, also known as polymersomes, are self-assembled polymer shells composed of block copolymer amphiphiles such as polyethylene glycol-polylactic acid (PEG-PLA) and PEG-polycaprolactone (PEG-PCL) (Figure 2 D). Block copolymers have the same basic amphiphilic property as lipids but they consist of distinct polymer chains covalently linked in a series of two or more segments [48]. Polymeric micelles differ from nanoparticles that are either more solid or monolithic (nanospheres) or contain an oily or aqueous core and are surrounded by a polymer shell (nanocapsules). However, in practice, polymeric micelles also be referred to as nanoparticle or nanocarriers because of their particle size.

3.4 Other novel nanocarriers: dendrimer, nanoemulsion and nanosuspension

Other nanocarriers recently used for brain drug delivery include: dendrimers, nanoemulsions and nanosuspensions. Dendrimers consist of repeating monomer units that form highly branched structures [49]. They are dispersed systems formed by well-controlled cross-linking of polymer molecules (Figure 2 C). Dendrimers possess internal nanostructures for entrapment of several therapeutic agents [50-53]. Nanoemulsions are dispersed systems consisting of nanoscale oil droplets. They solubilize lipophilic compounds well and are highly biocompatible. Considering that many oils used for nanoemulsion are edible (e.g. flaxseed oil), this class of nanocarriers are particularly appealing for oral administration [54-57]. Nanosuspensions are dispersed formulations of very fine particles or crystals of drugs. They are often developed for highly lipophilic compounds which can be hardly dissolved for efficient delivery. The solid drugs can be homogenized, dispersed and stabilized with surfactants to form nanosuspensions. The large effective surface area of the fine drug crystals can help increase their bioavailability both to the systemic circulation and the brain [58,59].

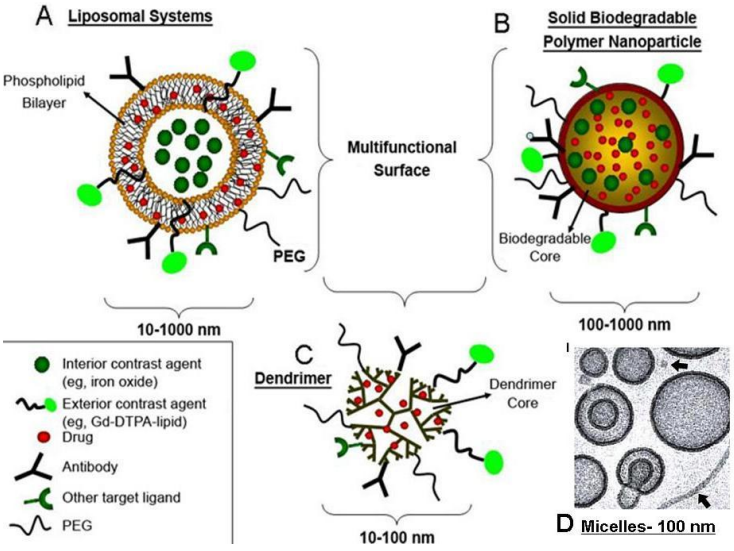

Figure 2. Various novel drug delivery systems for brain targetting

4. ADVANCED STRATEGIES DRUG DELIVERY TO BRAIN

4.1 Active targeting strategies

Nanocarriers can cross the BBB via receptor-mediated transcytosis, but this process is often inefficient. By modifying these systems with "targeting molecules" such as monoclonal antibodies, cellpenetrating peptides and/or receptor substrates, their drug delivery to brain can be significantly improved. Overall, significant improvement in CNS specificity and transcytosis efficiency has generally been achieved with the use of these systems.

4.2 Alternative strategies for brain delivery

In addition to targeted delivery, several alternative strategies have been developed to improve brain drug delivery by nanomedicine like efflux transporter inhibition [60,61], nanocarrier cationization [62], paracellular transport enhancement [63], intranasal administration [64], focused ultrasound and microbubbles with nanoparticles [65]. The brain and the nasal cavity are connected by the olfactory or trigeminal nerve system that terminates at the olfactory neuroepithelium or respiratory epithelium [64]. These two nerve systems can serve as the externally accessible points of the brain, and be exploited to bypass the BBB for direct nose-to-brain drug delivery. Along with this a number of groups have investigated enhanced delivery of drugs and antibodies using MRI-guided focused ultrasound with microbubbles and reported promising results. Despite these positive results and studies showing that ultrasound-induced BBB disruption does not cause substantial vascular damage that would result in ischemic or apoptotic death to neurons, there remain concerns over the safety of this strategy [65].

5. CONCLUSION

Now days, scientists have tremendous attention and effort focused on the development of modern and novel drug delivery systems to circumvent the BBB. This is due to the significant challenge faced by industry, government and academics in seeking effective drug therapies for the increasing incidence of brain disease associated with an ageing population. The present review is focused on various brain barriers and strategies to deliver the drug to the brain. Nanotechnology can provide exciting opportunities for improved therapeutic management of CNS diseases. To overcome the barriers in the brain novel drug delivery systems can be utilized, which ultimately will transport a drug to a diseased brain. Targeted delivery is likely the main research direction of CNS nanomedicine. Ideally, the ligand should be brain specific, or at least interact preferentially the receptors expressed at the BBB. With the availability of more specific and efficient targets, the development of safer and effective CNS-targeting nanomedicine will be facilitated. Therefore, it is concluded that employing the multidiscipline approach with innovative ideas the targeted drug delivery to brain can be achieved and thus reaching the ultimate goal of delivering drug therapy, selectively and efficiently, across the BBB.

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