RECENT ADVANCEMENT IN DRUG DELIVERY SYSTEM FOR BRAIN: AN OVERVIEW

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ABSTRACT

The brain is one of the most complex and magnificent organs in the human body. It is the organ that controls most of the activities of the body. The central nervous system [CNS], efficiently isolated from the systemic circulation by the presence of two barrier systems: the blood brain barrier [BBB] and the blood cerebrospinal fluid barrier [BCSFB]. These two barrier shielded the brain against potentially toxic substances. Unfortunately, the same mechanisms that protect it against intrusive chemicals can also frustrate therapeutic interventions. Therefore drug delivery to the Central Nervous System [CNS] in treatment of CNS related disorders is very complicated and challenging. Although some neuropharmaceutical agents have great potential for treating CNS disorders, major challenge to CNS drug delivery is the Blood Brain Barrier [BBB], which limits the access of drugs to the brain. Progress in brain drug delivery has lagged behind other areas because of the restrictions posed by the BBB. Only a small class of drugs—small molecules with high lipid solubility and a low molecular mass of < 400–500 Daltons [Da]—actually cross the BBB. However, there are only a few diseases of the brain that consistently respond to this category of small molecules. This review encompasses detailed discussion of some of the recent drug delivery systems like Dendrimers, Polyanhydrides, Lipoplexes, Polyplexes, Scaffolds, Convection-enhanced delivery, and Modified nanoparticles for targeting drugs to the brain.


INTRODUCTION

Brain is the most important organ of human body, which tends to controls all body functions. For accomplishing drug delivery to the brain it is necessary for the drug molecules to get pass
the blood brain barrier. This take into account the brain’s complex anatomy as well as the restrictions imposed by the Blood Brain Barrier.\[1\]

Drug delivery for the treatment of CNS-related disorders is very complicated and challenging process. The main reason for this is that the drugs are to able to get pass the brain capillary wall, which in conjunction forms the blood–brain barrier [BBB] in vivo. Only small molecules with high lipid solubility and a low molecular mass of < 400–500 Daltons [Da]—actually can cross the BBB. However, there are only a few diseases of the brain that respond to small molecules, and these include chronic pain, depression, affective disorders, and epilepsy. Diseases like Alzheimer disease, stroke/neuroprotection, brain and spinal cord injury, brain cancer, HIV infection of the brain, various ataxia-producing disorders, amyotrophic lateral sclerosis [ALS], Huntington disease, and childhood inborn genetic errors affecting the brain are not affected by the small drug molecule classes.\[1\] Although Ldihydroxyphenylalanine [L-Dopa] therapy has been available for decades to treat PD, there has been no neuroprotective drug for PD that halts the inexorable neurodegeneration of this common disorder. Many of the CNS disorders that are refractory to small-molecule drug therapy might be treated with large-molecule drugs including recombinant proteins and gene based medicines however, several hindrances, biochemical and economic, are inhibiting their development. To provide a drug to brain is not possible with conventional drug delivery system. By using targeted drug delivery system we can easily cross BBB and can deliver drug up to brain.\[1\] Drugs can be administered directly into the CNS or administered systemically for targeted action. Progress in brain drug delivery has lagged behind other areas because of the BBB. Advanced techniques and technological developments have helped in understanding of the cell biology of the BBB and thus have created newer ways for improved drug delivery to the CNS.\[1\]

**Barriers to CNS drug delivery**

The drug delivery to the brain for the successful treatment of the brain disease is very challenging, because of its barriers present in it. The most limiting factor to successful treatment of brain disease is the blood-brain barrier [BBB] which prevents access of approx. 98% of current pharmaceutical agents to the brain when delivered intravenously.\[2\]

**Blood brain barrier**

Blood-Cerebrospinal Fluid Barrier.
Blood brain barrier
The term “blood brain barrier” was first coined in 1900 by Lewandowsky, while studying the limited penetration of potassium Ferro cyanate into the brain.\textsuperscript{[2]} BBB makes themost important part of the natural mechanism active in protection of the brain from exposure to potential hazardous xenobiotics. It has some distinguishing features causing highly effective impediment for the entry of chemical compounds into CNS\textsuperscript{[2]}. The BBB is different from the barriers between the peripheral vasculature and other organs in the body due mainly to the presence of tight junctions between adjacent endothelial cells.\textsuperscript{[2]} The CNS consist blood capillaries which are structurally different from the blood capillaries in other tissues; these structural differences result in a permeability barrier between the blood within brain capillaries and the extracellular fluid in brain tissue. Capillaries of the vertebrate brain and spinal cord lack the small pores that allow rapid movement of solutes from circulation into other organs; these capillaries are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions. Tight epithelium, similar in nature to this barrier, is also found in other organs skin, bladder, colon, and lung]. This permeability barrier, comprising, the brain capillary endothelium, is known as the BBB.\textsuperscript{[3]}

Blood cerebrospinal fluid barrier
The second barrier, located at the choroid plexus, is represented by the blood-cerebrospinal fluid barrier [BCSFB] that separates the blood from the cerebrospinal fluid [CSF] which, in turn, runs in the subarachnoid space surrounding the brain.\textsuperscript{[4]} CSF can exchange molecules with the interstitial fluid of the brain parenchyma; the passage of blood-borne molecules into the CSF is also carefully regulated by the BCB. Physiologically, the BCB is found in the epithelium of the choroids plexus, which is arranged in a manner that limits the passage of molecules and cells into the CSF.\textsuperscript{[4]} The choroid plexus and the arachnoid membrane act together at the barriers between the blood and CSF. The arachnoid membrane is generally impermeable to hydrophilic substances, and its role is formation of the Blood-CSF barrier, is largely passive. The choroid plexus forms the CSF and actively regulates the concentration of molecules in the CSF.\textsuperscript{[4]}
Factors that affect the drug transport across BBB

- Concentration gradient of drug/polymer
- Molecular weight of the drug
- Lipophilicity of the drug
- Pathological status
- Affinity for efflux proteins
- Molecular charge
- Cerebral blood flow
- Clearance rate of drug/polymer
- Cellular enzymatic stability\(^{[4]}\)

Transport across blood brain barrier

Different mechanisms used to cross the BBB are shown in Fig.

- Small hydrophilic molecules such as amino acids, glucose, and other molecules necessary for the survival of brain cells use transporters expressed at the luminal [blood] and basolateral [brain] side of the endothelial cells.
- Larger and/or hydrophilic essential molecules such as hormones, transferrin for iron, insulin, and lipoproteins use specific receptors that are highly expressed on the luminal side of the endothelial cells. These receptors function in the endocytosis and transcytosis of compounds across the BBB.
- Small lipophilic molecules can diffuse passively across the BBB into the brain but will be exposed to efflux pumps [P-glycoprotein].\(^{[4]}\)
Brain related diseases
The brain is the center of the nervous system. CNS related disorders are of two type Diseases with prominent neurodegeneration - Neurodegenerative disorders embrace chronic neurodegenerative disorders that lead to dementia, Alzheimer’s disease, frontotemporal lobar degeneration, multi-infarct dementia, disorders of movement, Parkinson’s disease and Huntington’s disease etc.

Diseases without neurodegeneration - CNS disorders without evident neurodegenerative pathology embodies a heterogeneous group of disorders including anxiety, depression, schizophrenia, epilepsy, insomnia, autism, brain tumors [most fatal] and many others.\(^4\)

Approaches for brain targeted drug delivery
To overcome the multitude of barriers restricting CNS drug delivery of potential therapeutic agents, numerous drug delivery strategies have been developed.

These strategies generally include following categories:

A. **Non-invasive**
   - Chemical techniques
     a. Prodrug
   - Colloidal Techniques
     a. Nanoparticles
     b. Liposomes
   - Biological method
B. Invasive
   a. Intracerebroventricular [ICV] infusion
   b. Intra-cerebral injection or implants
   c. Disruption of the BBB

C. Miscellaneous techniques
   a. Intranasal delivery

D. Recent advances in brain targetting
   a. Micelles
   b. Dendrimers
   c. Polyanhydrides
   d. Scaffolds
   e. Convection-enhanced delivery

Non–invasive approach

Chemical technique

Prodrug \(^{[5]}\)
Drug is converted into prodrug by chemical modification so that it reach to the specific place at specific to cure the disease. Prodrug is an inactive form of the drug which when reach to the target site is conveted into the active form.\(^{[5]}\) This is done by the multistep enzymatic activation and chemical transformation. Brain is an organ which only allow small and lipophillic molecule through the blood brain barrier so that lipophobic molecule can enter the brain by prodrug approach. The lipophillic compound enter the brain as prodrug and converted into the lipophobic compound which will not able to exit and it will locked in the brain. Therefore treatment efficiency is increased.\(^{[5]}\)

Examples
levodopa, GABA, Niflumic acid, valproate.

Colloidal Techniques

a. Liposome
Liposomes or lipid based vesicles are microscopic [unilamellar or multilamellar] vesicles that are formed as a result of self-assembly of phospholipids in an aqueous media resulting in closed bilayered structures. The phospholipid bilayered membrane encloses aqueous core
which encapsulate the water soluble compound and lipid soluble compounds get entrapped in the bilayered membrane. Therefore, both water and lipid soluble drugs can be successfully entrapped into the liposomes. Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2 and interferon-γ. Liposomes reduced toxicity and increased stability of entrapped drug via encapsulation [eg. Amphotericin B, Taxol]. Brain cannot synthesize glucose which is an essential nutritional substance for the brain functions. It is transported by the glucose transporter by the brain capillary endothelial cells. Liposome showed better result in the transportation of the glucose.[5]

b. Nanoparticle
Nanoparticles [NPs] are solid colloidal particles made up of polymeric materials ranging in size from 1-1000 nm. NPs can be divided into two classes:

Nanocapsules [core-shell structure] [reservoir system] pharmaceutical ingredient encapsulated inside the core.

Nanospheres [matrix structure] pharmaceutical ingredient entrapped in the matrix.

Now a days, NPs are gaining good interest as carriers for the drugs which are delivered to the brain. This is because NPs offer more stability to the encapsulated drug in biological fluids and against enzymatic metabolism as compared with other colloidal systems. NPs are rapidly cleared from the blood following intravenous administration. As carriers for drug delivery to the brain, NPs need to be small [<100 nm] to avoid the RES, neutrophil activation, platelet aggregation, and inflammation. When the drug is delivered to the brain is in the SLNs then the concentration of the drug is higher as compared to the other.[5]

Biological methods
Biological approaches of CNS drug delivery primarily emanate from the understanding of the physiological and anatomical nuances of the BBB transportation. Of the many available approaches, conjugation of a drug with antibodies is an important mechanism. Other biological methods for targeting exploit ligands in the form of sugar or lectins, which can be directed to specific receptors found on cell surfaces. The antibody-drug conjugate is directed towards an antigen residing on or within the target tissues. Antibodies are particularly well
suited for targeting BBB receptor-mediated transcytosis systems given their high affinity and specificity for their ligands.\textsuperscript{[5]}

**B. Invasive Approach**

*a. Disruption of the blood brain barrier*

This technique is used to circumvent the blood brain barrier for therapeutic purpose. The disruption of the blood brain barrier is done by injecting the sugar solution [mannitol] into the arteries in the neck. This result in the leakage of the tight junction of the blood brain barrier. This method allows the delivery of chemotherapeutic agents in patients with malignant glioma, cerebral lymphoma and disseminated CNS germ cell tumours, with a subsequent decrease in morbidity and mortality compared with patients receiving systemic chemotherapy alone.\textsuperscript{[6]}

- **Osmotic disruption**

Transient osmotic disruption of the blood-brain, blood-CSF, and blood-tumor barriers can be achieved throughout a vascular circulation by intraarterial infusion of a hyperosmotic agent\textsuperscript{[6]}

Due to these agents, endothelial cells of the BBB losses water and resulting in shrinkage. Therefore the tight junction become leaky and the BBB is permeable to exogeneous substances.\textsuperscript{[7]}

The mechanism by which the osmotic agents disrupt the BBB are First, water is drawn out of the endothelial cell and into the blood vessel lumen, causing shrinkage of the endothelial cells. Secondly, the net flow of water out of the brain leads to vasodilation, thereby stretching the endothelial cell membrane. Lastly, interactions between actin and cadherin cause the endothelial cell cytoskeleton to contract via a calcium-dependent mechanism. Each of these mechanisms places stress on the tight junctions that join the endothelial cells, ultimately causing widening of the junctions and allowing paracellular transport into the brain parenchyma.\textsuperscript{[7]}

- **Focused ultrasound BBB disruption technique**

FUS is a valuable method for the BBB disruption technique. This technique has several advantages over other approaches because it is readily repeatable, noninvasive, and able to disrupt the BBB in a targeted way. FUS may increase cerebrovascular permeability by producing shear stress in cells or by activation of signaling pathways involved in the regulation of permeability. Microbubbles can be used with this method to lower the ultrasound energy required to induce disruption of the blood brain barrier. Microbubbles are
administered intravenously and these enhanced FUS resulting disruption of BBB with less side effect.\textsuperscript{[8]}

Po-Hung Hsu \textit{et al} evaluate the local, targeted delivery of rAAV vectors into the brains of mice by noninvasive, reversible, microbubble-facilitated focused ultrasound [FUS], resulting in BBB opening that can be monitored and controlled by magnetic resonance imaging [MRI]. They found that IV-administered AAV2-GFP [green fluorescence protein] with a low viral vector titer [16109 vg/g] can successfully penetrate the BBB-opened brain regions to express GFP.\textsuperscript{[9]}

\textbf{b. Intracerebroventricular [ICV] infusion}

The most direct way of circumventing the BBB is to deliver drugs directly to the intraventricular, intracavitary, or interstitial system.\textsuperscript{[10]} Drugs can be infused intraventricularly using an Ommaya reservoir, a plastic reservoir implanted subcutaneously in the scalp and connected to the ventricles within the brain via an outlet catheter. Drug solutions can be subcutaneously injected into the implanted reservoir and delivered to the ventricles by manual compression of the reservoir through the scalp. Clinical examples of intrathecal small drug delivery are the ICV administration of glycopeptide and aminoglycoside antibiotics in meningitis, the intraventricular treatment of meningeal metastasis, intrathecal injection of Baclofen for treatment of spasticity and the infusion of opioids for severe chronic pain.\textsuperscript{[10]} These method considered the most important method for the treatment of tumor occurs in the brain. However, this strategy has certain disadvantages, including CNS infection, catheter obstruction, and inadequate drug distribution.

c. \textbf{Intra cerebral implants}

Intra cerebral implants is an approach mainly used in case of malignant gliomas. Drug added to this polymeric implants, that intracranically bypass the BBB and release the drug at specific target site in a sustained manner. The basuc mechanism is diffusion. Therefore. Distribution in the brain by diffusion is decreased exponentially with distance. So that the implants is placed in exact that site where the drug is require to get good efficacy. Malignant gliomas are deeply in the brain and thus the effectiveness of the drug delivered by polymers is dependent on whether drug molecule can be transported to the sufficient distance from the implanted site to reach malignant giomas.\textsuperscript{[11]}
C. Miscellaneous techniques

Intra nasal drug delivery
In this approach drug is delivered through the nasal cavity. Intranasal drug delivery is the approach in which the drug transported along with olfactory neuron to the CSF and olfactory bulb. The drug absorption to the systemic circulation by respiratory epithelium. Its is significantly faster route for direct nose-to brain transfer, where by compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the subarachnoid space and in direct contact with the CSF.\textsuperscript{[12]}

Recent advances in brain targetting
Convection Enhanced Delivery
CED is a noval approach for the drugs which are used for the brain tumors. In this method the drug is infused via intra tumoral or inta perenchymal catheters continuously\textsuperscript{[13]} A continuous infusion pressure gradient over hours to days results in distribution of therapeutic agents into the interstitial space. The CED technique is used primarily for large molecular weight agents that show minimal leakage across the BBB and/or have significant systemic toxicity, including viruses, oligonucleotides, nanoparticles, liposome, and targeted immunotoxins. Parameters that affect CED volume of distribution include infusion parameters [rate, volume, duration, cannula size], infusate characteristics [molecular weight, surface properties, tissue affinity], and tissue properties [tissue density, extracellular space, vascularity, and interstitial fluid pressure].\textsuperscript{[8]} CED is a promising approach for the delivery of various agents including conjugates, monoclonal antibodies, antisense oligonucleotides or viral vectors CED has also been applied in antibody-mediated therapies and immunotherapies with acceptable toxicities yet highly variable efficacy. Additional hurdles of CED include limited distribution area, the requirement for surgery, high infusion rates and difficulty in real-time monitoring\textsuperscript{[13]}

Polymeric micelles
Surfactant molecules when aggregated then it is called micelles. A typical micelles has a hydrophillic head and an hydrophobic tail region in the micelle centre.\textsuperscript{[14]} The use of micellar solutions of low molecular weight surfactants has been one of the popular methods for the solubilization of hydrophobic drugs; however, such surfactants suffer from high critical micelle concentration and concomitant low stabilities. In contrast to surfactants of low molecular masses, polymeric micelles are associated with general advantages like higher stability, tailorability, greater cargo capacity, non-toxicity and controlled drug release.
Polymeric micelles as drug delivery vehicles. By restricting drug transport to the brain, the blood brain barrier [BBB] is challenging for treatment of brain tumors and neurodegenerative diseases, such as HIV-associated dementia, stroke, Parkinson’s and Alzheimer’s diseases. Two strategies using polymer micelles have been evaluated to enhance delivery of biologically active agents to the brain. The first strategy is based on modification of polymer micelles with antibodies or ligand molecules capable of transcytosis across brain microvessel endothelial cells comprising the BBB. The second strategy uses Pluronic block copolymers to inhibit drug efflux systems, particularly Pgp, and selectively increase the permeability of BBB to Pgp substrates.\[14\]

**Dendrimer**

The term dendrimer is derived from Greek words “Dendron” meaning trees or branches and “meros” meaning part. Dendrimer is a highly branched polymer molecule formed by a central core to which the branches are attached, the dendrimers have three components.

**Core part**

**Interior branches**

**Exterior branches**

They are of small size comparable to that of polymeric micelles or nanoparticles of small dimensions. Dendrimers used in targeted drug delivery are usually 10-100 nm. Thus, for instance, a typical dendrimer molecule, such as poly[amidoamine] [PAMAM] dendrimer, has a diameter ranging from 1.5 to 14.5 nm. As carriers for drug delivery to the brain, dendrimers conjugates with anti-cancer agents have been studied for the treatment of tumors at CNS level. In addition, gene delivery into brain has been also shown using a transferring conjugated PEG modified PAMAM dendrimer.\[15\]

**Pолананидрид**

Polyhydrides are the molecule in which the drug is embedded into the biodegradable polymeric matrix. These are the molecule which release the drug by simple hydrolysis. Since these are the bio degradable polymers, they degrade uniformly into non-toxic metabolites that are non-inflammatory, non-mutagenic and non-cytotoxic. Their degradation profile can be modulated from days to months by varying the type and ratio of the monomers. Polyanhydrides are basically intracerebral implants useful for controlled drug delivery. Brain tumor Glioblastoma multiforme [GBM] accounts for about 80% of adult primary brain tumors and are usually found in the cerebral hemispheres. Many of the anti-cancer drugs have
large molecular structures, ionic charge or are hydrophilic and thus are unable to cross the BBB, and intolerably high systemic levels are required to achieve the therapeutic doses within the CNS. Use of polyanhydrides for direct localized delivery is one of the simplest approaches.\textsuperscript{16}

**Scaffolds**

Scaffolds is an implants which can be used to treat various disease of the brain, including replacing tissue lost to traumatic brain injury [TBI], delivering drugs to help treat neurological diseases such as Parkinson’s and Alzheimer’s, as well as serving as coatings for brain-implanted devices to limit inflammation. Current treatment for TBI focuses on preserving the healthy tissue remaining after injury as opposed to attempting to regenerate damaged tissue. Replacing damaged tissue with scaffolds containing drugs could help promote regeneration and functional recovery. Delivery of therapeutics from scaffolds could potentially help limit damage to neurons while helping to preserve function that would normally be lost to these diseases. Finally, drug releasing coatings for brain-implanted devices can improve their function by allowing them to record signals from neurons for longer time periods.\textsuperscript{17} Delivery of therapeutic agents from scaffolds potentially helps to limit the damage to neurons while helping to preserve their function.

**Considerations include**

- Minimizing cell death and inflammation after implantation of scaffolds, by choosing biocompatible materials
- Controlling drug release over an appropriate time period to prevent multiple surgeries or injections
- Making the whole process minimally invasive to preserve the integrity of the BBB
- Scaffolds should be small and minimally invasive\textsuperscript{17}

**CONCLUSION**

For the treatment of the CNS related disorder, the delivery of drug molecules to the brain is very complex and challenging because of the variety of physiological, metabolic and biochemical obstacles called BBB,BCB and BTD. Due to the lack of specific and efficacious approaches for the delivery of the drug to the CNS for the effective treatment id not satisfactory.
Now recent developments have done in drug delivery strategies which have been proven to be helpful to overcome barriers associated with brain drug delivery. Nanotechnology and various other delivery system can be further explored for their great potential in penetration the BBB efficiently. The ability of engineered liposomes to enter into brain tumors makes them potential delivery systems for brain targeting. A technology of chimeric peptides which are potential BBB transport vectors and have been applied to several peptide pharmaceuticals, nucleic acid therapeutics, and small molecules to make them CNS transportable.

REFERENCES


