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## A Review on Drug Molecules Targeting to Brain

Divya Jyothi Uppari

Jawaharlal Nehru Technological University, Hyderabad - 500 085, Telangana, India

### Review Article

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#### \*For Correspondence

Jawaharlal Nehru Technological  
University, Hyderabad, Telangana  
500085, India. E-mail:  
[divyauppari@rediffmail.com](mailto:divyauppari@rediffmail.com)

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#### ABSTRACT

The blood-brain barrier (BBB) represents a noteworthy obstruction for drug conveyance to the brain. Numerous therapeutics with potential for treating neurological conditions demonstrate inconsistent with intravenous conveyance simply because of this barrier. As opposed to adjusting drugs to infiltrate the BBB accurately, it has demonstrated more effective to either physically bypass the barrier or to utilize particular conveyance vehicles that evade BBB regulatory systems. The advancement of new drugs for the brain has not kept pace with advancement in the atomic neurosciences in light of the fact that the larger part of new drugs found don't cross the blood-brain barrier (BBB). This review deals in short about the status of the BBB, distinctive pathologies of cerebrum like neurodegenerative, cerebrovascular and inflammatory diseases. The primary piece of this subject expects to audit the significance of BBB and convey drugs into the cerebrum. The use of nano-technology and liposomes as mainly used to target various CNS disorders. The later part of this topic contains future aspects of brain drug targeting and some patents of drugs.

#### REVIEW ARTICLE

#### Introduction

The advancement of new drugs for the mind has not kept pace with advancement in the molecules neurosciences, in light of the fact that the larger part of new drugs found don't cross the blood-brain barrier (BBB) [1]. Now a day target delivery of drug molecules to brain is one of the most exacting researches filed in pharmaceutical sciences [2,3]. The blood-brain barrier (BBB) represents an impediment for a huge number of drugs, including antibiotics, antineoplastic agents [4-6], and a variety of central nervous system (CNS)-active drugs, especially neuropeptides. Therefore, different scenarios have been proposed to increase the outcome of various drugs to this tissue which adds colloidal drug carriers, liposomes, nanoparticles and olfactory route of administration and nano-technology [7-10]. This review deals in short about the status of the BBB, distinctive pathologies of cerebrum like neurodegenerative, cerebrovascular and inflammatory diseases. The primary piece of this subject expects to audit the significance of BBB and convey drugs into the brain. The use of nano-technology and liposomes as mainly used to target various CNS disorders. The later part of this topic contains future aspects of brain drug targeting and some patents of drugs [11-12].

#### Importance of Brain Targeting System

- The worldwide business sector for medications for the central nervous system (CNS) is extraordinarily immature and would need to develop by more than 500% fair to be equivalent to the worldwide business sector for cardiovascular drugs [13, 14]. The guideline purpose behind this being worked on of the worldwide brain drug business is that the immense greater part of drugs doesn't cross the brain narrow divider, which frames the blood-brain barrier (BBB) in vivo.

- The blood-brain barrier (BBB) represents an impediment for a huge number of drugs, including antibiotics, antineoplastic agents, and a variety of central nervous system (CNS)-active drugs, especially neuropeptides. Blood-Brain Barrier is located at the level of brain capillaries, where there is a concurrence of various cell types; Oligodendroglia, pericytes, astrocytes and microglia [15-20].
- The brain micro vessel endothelial cell (BMEC) that form the blood-brain barrier, show essential morphological attributes, for example, the vicinity of tight intersections between the cells [21-23], the nonappearance of fenestrations and a decreased pinocytotic action, that together help to limit the entry of mixes from the blood into the additional cell environment of the brain [24,25].
- Each slender vessel is bound by a solitary layer of endothelial cells, associated by tight intersection, subsequently making it extremely troublesome for most molecules to leave the vessels and penetrate into the brain. Tight intersections give huge transendothelial electrical resistance (TEER) to BMEC and obstruct the entrance of potential restorative operators such as oligonucleosides, antibodies, peptides and proteins. Besides, BMEC express a mixed bag of catalysts, both cytosolic and on the additional cell film which additionally add to the prohibitive way of the BBB.
- P-glycoprotein (P-gp) is also present in the luminal plasma membrane of BMEC [26-28].

## Brain Disorders

### *Meningitis*

Meningitis is an inflammation of the meninges. The meninges are the slender layers of tissue that cover the brain and the spinal cord. Meningitis is most ordinarily genesis about by infection (by bacteria, viruses, or fungi). It can likewise be created by draining into the meninges, malignancy, infections of the resistant systems, and different factors. The most unsafe types of meningitis are those brought about by bacteria. The disease is intense and can be lethal [29-31].

### *Encephalitis*

Encephalitis implies an inflammation of the cerebrum. This inflammation of the brain brought on by the viral and bacterial disease. Both the brain and spinal cord are included, encephalomyelitis issue. Encephalitis ranges from gentle to extreme which may bring about changeless neurological harm and death.

Encephalitis is an uncommon illness. It happens in more or less 0.5 every 100,000 people. It is most normal among in kids and individuals with debilitated immune systems. A few individuals who have encephalitis are left with unceasing brain damage [32-37].

## Anatomy of Blood Brain Barrier

An anatomic-physiologic highlight of the brain thought to comprise of walls of vessels in the focal sensory system and encompassing astrocytic glial layers.

The boundary isolates the parenchyma of the focal sensory system from blood (Figure 1). The blood brain barrier anticipates or moderates the entry of a few drugs and other substance mixes, radioactive particles, and infection creating organic entities, for example, infections from the blood into the central nervous system [38-42].

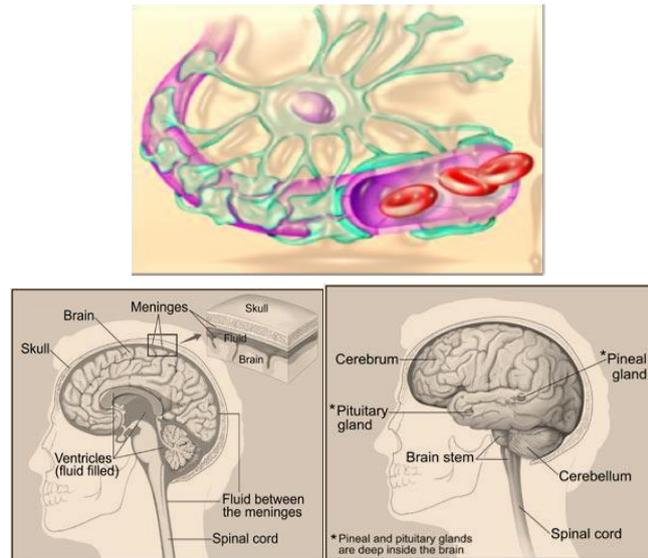


Figure 1. a. schematic diagram of Blood Brain Barrier, b. The brain and nearby structures, c. Major parts of the brain

### Importance of the Barriers

- Blood Brain Barrier
- Blood-Cerebrospinal Fluid Barrier
- The Nose-Brain barrier
- Arachnoid matter cerebrospinal fluid barrier

Without the BBB, undesirable molecules could unreservedly diffuse from the vessels to the liquid that encompasses the brain cells

- These undesirable molecules include:

**Toxins:** Substances created by plants and animals that are poisonous to humans [43].

**Ions:** Atoms with extra electrons or missing electrons.

**Acids and Bases:** Common solutions that exist everywhere, almost every liquid that we encounter in our daily lives consists of acidic and basic properties, with the exception of water. They have completely different properties and are able to neutralize to form H<sub>2</sub>O, which will be discussed later in a subsection [44-46].

- The BBB also incorporates mechanisms to transport certain substances in:

**Glucose:** The universal energy source, which is needed by every cell in your body.

**Oxygen:** Electron acceptor par excellence, do without it and die.

**Certain Ions:** Cations, Anions, Chlorine, Calcium, etc. Involved in nervous system transmission [47].

- The BBB also lets various substances in because it either can't pump them out or its mechanisms can't tell the difference between them and one of the substances that it naturally transports across:  
Ethanol- enters by the same pathways that let glucose in, which is why drinking alcohol affects the brain. Vitamin C, Nicotine, Caffeine [48,49].

## Multiple Functions of Blood Brain Barrier

### 1) Function as an active pump:

Binding of a substrate and ATP molecule happen at the same time. Taking subsequent to tying, ATP hydrolysis moves the substrate into a position to be discharged from the cell. Arrival of the phosphate (from the first ATP atom) happens simultaneously with substrate discharge. ADP is discharged, and another particle of ATP ties to the optional ATP-tying site. Hydrolysis and arrival of ADP and a phosphate molecule resets the protein [50-52].

### 2) Function as metabolite barrier:

5-HTP promptly crosses the blood-brain barrier and moreover is quickly decarboxylated to serotonin (5-hydroxytryptamine or 5-HT) and hence may be valuable for the treatment of wretchedness. However serotonin has a moderately short half-life since it is quickly metabolized by monoamine oxidase, and hence is liable to have restricted adequacy.

### 3) Rate-limiting role of the BBB in brain drug development:

Present-day incongruities in brain drug advancement are shown by a thought of a portion of the attributes of the CNS drug industry. Though 98% of all little atom medications don't cross the BBB, and about 100% of large-molecule drugs don't cross the BBB, with a few studies having co infused Polysorbate 80, a cleanser that can disturb the BBB, with the drug as a balancing out specialists, and erroneously ascribing the cleanser impacts to their own particular nanoparticles. In different studies, the large size of the liposomes that were used produced micro embolism that gave a bogus impression of brain uptake [53-64].

## Drug Transport through Blood Brain Barrier

- Carrier-mediated transport can likewise be partitioned into various distinctive instruments subject to vitality and/ or co-transport of another substance. Co-transport may be in the same bearing (symport) or the other way (antiport). This procedure continues from a district of high fixation to an area of low focus.
- Endocytosis can be isolated into bulk-phase, otherwise called fluid phase endocytosis and intervened endocytosis (receptor and absorptive interceded).
- Bulk-phase endocytosis (pinocytosis) is the nonspecific uptake of extracellular liquids and happens at a constitutive level inside of the cell by means of systems, which are autonomous of ligand tying. Bulk-phase endocytosis is temperature and vitality subordinate, non-focused, and non-saturable. Bulk-phase endocytosis strikes an extremely restricted degree in the endothelial cells of the cerebral microvasculature [65-69].
- Receptor-intervened endocytosis (RME) gives an intends to particular uptake of macromolecules. Cells have receptors for the uptake of a wide range of sorts of ligands, including hormones, development variables, compounds, and plasma proteins. RME happens at the brain for substances, for example, transferrin, insulin, leptin and IGF-I & IGF and is a profoundly particular sort of vitality ward transport.
- Absorptive-intervened transport (AME) is activated by an electrostatic connection between an emphatically charged substance, as a rule a charge moiety of a peptide, the contrarily charge plasma membrane surface (i.e. glycocalyx). AME has a lower fondness and higher limit than receptor-intervened endocytosis [70-76].

## Factors Affecting Drug Permeation through Blood Brain Barrier

Drug absorption depends on the lipid solubility of the drug, its formulation and the route of administration.

- A drug needs to be lipid solvent to infiltrate membranes unless there is a dynamic transport system or it is small to the point that it can go through the fluid diverts in the membrane.
- Traditional oral or parenteral organization may not accomplish ideal restorative concentrations of drug at its site of activity. After oral organization, metabolism system of the drug in the gut or liver may bring about low systemic bioavailability. Modern technology has created conveyance systems that permit exact control of drug data into the body by more unorthodox routes.

### Strategies of Brain Drug Delivery System

- The blood- Brain Barrier (BBB) remains a noteworthy obstruction to the effective conveyance of drug to treat central nervous system (CNS) issue. Specialists are investigating an assortment of ways to deal with protect the capacity of the BBB to square unsafe and poisonous substances from entering the brian and to allow the section of viable pharmaceuticals for the treatment of CNS. "The key test is to treat individuals experiencing CNS issue while attempting to stay consistent with the doctor's oath,'Firstdonoharm'." [77]
- One innovation for empowering dynamic transport of little atom medicates over the BBB includes focusing on endogenous supplement transporters. These transporters are individuals from the solute carrier (SLC) transporter super gang. Transport of little particles over the BBB by these layer proteins is known as transporter mediated transport (CMT) [78-80].
- Another major system that is utilized as a part of typical mammalian physiology to empower required molecules to cross the BBB is receptor- mediated transport (RMT). The brain utilizes RMT to transport proteins, peptides, and lipoproteins that are required for brain work over the BBB. Examples of biomolecules that are transported into the cerebrum by means of RMT incorporate insulin, insulin-like growth factor (IGF), leptin, transferrin, and low-density lipoprotein (LDL) [81-84].

### Methods for Brain Delivery Strategies

Several drugs don't have satisfactory physiochemical qualities, for example, high lipid dissolvability, low molecular size and positive charges which are vital to succeed in crossing BBB

#### 1) Neurosurgical/Invasive strategies:

- **Disruption of the BBB: -**

The idea behind this methodology was to separate the obstruction quickly by infusing mannitol arrangement into courses in the neck. The subsequent high sugar fixation in brain capillaries takes up water out of the endothelial cells, contracting them in this way opening tight intersection [85-87]. The impact goes on for 20-30 minute, amid which time drugs diffuse uninhibitedly, that would not typically cross the BBB. This technique allowed the conveyance of chemotherapeutic agents in patients with cerebral lymphoma, threatening glioma and spread CNS germ cell tumors [88-89].

- **Intraventricular / Intrathecal delivery: -**

Here utilizing a plastic repository which embedded subcutaneously in the scalp and associated with the ventricles inside of the brain by an outlet catheter. Drug injection into the CSF is a suitable technique for destinations near to the ventricles only.

- **Intra Nasal Drug Delivery: -**

At the point when a nasal drug plan is conveyed profound and sufficiently high into the nasal cavity, the olfactory mucosa may be come to and drug transport into the brain and/or CSF by means of the olfactory receptor neurons may occur.

## 2) Pharmacological Based Strategies:

- **Colloidal Drug Carriers:-**

Colloidal drug carrier systems, for example, micellar arrangements, vesicle and liquid crystal dispersions, and nanoparticle scatterings comprising of little particles of 10- 400 nm width show incredible guarantee as drug delivery systems. The objective is to acquire systems with improved drug stacking and discharge properties, long time span of usability and low poisonous quality. The incorporated drug takes part in the microstructure of the system, and may even impact it because of molecular associations, particularly if the medication forces amphiphilic and/or mesogenic properties [90-93].



Figure 2: Types of Pharmaceutical Carriers

## Pharmaceutical Carriers

### *Micelles*

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in watery arrangements are of great enthusiasm for drug conveyance applications (Figure 2). The drugs can be physically captured in the center of block copolymer micelles and transported at fixations that can surpass their natural water-solvency [94-96]. Besides, the hydrophilic blocks can shape hydrogen bonds with the fluid surroundings and structure a tight shell around the micellar core. Subsequently, the substance of the hydrophobic core is adequately secured against hydrolysis and enzymatic debasement. Functionalization of block copolymers with cross linkable groups can expand the dependability of the relating micelles and enhance their temporal control [97-99].

### Block Copolymer Micelles

### *Liposomes*

In Liposomes, one end of every molecule is water solvent, while the inverse end is water insoluble. Water-dissolvable medicines added to the water were caught inside the conglomeration of the hydrophobic closures; fat-solvent pharmaceuticals were joined into the phospholipid layer [100] (Figure 3).

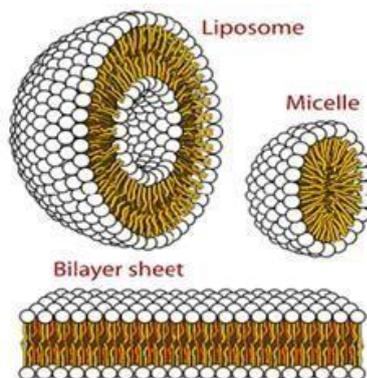


Figure 3: Liposomes, Micelles, Bilayer sheet

## Nanotechnology

### Nanoparticulate Systems for Brain Delivery of Drugs

Nanoparticles are polymeric particles made of regular or simulated polymers going in size between around 10 and 1000 nm (1  $\mu$ m). Drugs may be bound in form of a solid solution or scattering or be adsorbed to the surface or chemically attached.

Ex: Poly (butyl cyano acrylate) nanoparticles represent the only nanoparticles that were so far successfully used for the in vivo delivery of drugs to the brain. The first drug that was delivered to the brain using nanoparticles was the hexapeptidylarginine (Tyr-D-Ala- Gly- Phe-Leu-Arg), a Leu-enkephalin analogue with opioid activity [101-104].

The nanotechnology includes;-

- Coated nanoparticles
- Pegylated nanoparticles
- Solid Lipid nanoparticles (SLN)
- Nanogels

### Advantages of Nanotechnology

- Due to their little size nanoparticles enter into even small capillaries and are taken up inside of cells, permitting an effective drug aggregation at the focused on locales in the body [105].
- The utilization of biodegradable materials for nanoparticle preparation, permits maintained medication discharge at the focused in the vicinity after injection more than a time of days or even weeks [106].

### Physiologic Based Strategies

- Chimeric Peptide Technology

Chimeric peptides are framed when a drug that is typically not transported through the BBB, is conjugated to a drug-targeting vector. The recent is an endogenous peptide, modified protein, or peptidomimetic monoclonal antibody (mab) that experiences RMT (Rapid metabolic transfer) through the BBB on endogenous receptor systems, for example, the insulin receptor. Peptidomimetic mabs tie to exofacial epitopes on the BBB receptor that are expelled from the endogenous ligand tying site and cross the BBB on the endogenous RMT system inside of the BBB [107].

Ex: Brain drug delivery in rats is possible with the OX26 mouse mab to the rat tfr. Brain drug delivery in humans is possible with the genetically engineered chimeric HIR mab.

- **Neuroprotection with Peptide Radiopharmaceuticals**

The brain imaging practice utilizes small-molecule radio chemicals that tie to monoamine or amino corrosive neurotransmitter systems. Though there are less than a dozen monoaminergic or aminoacidergic neurotransmitter systems, there are several peptidergic neurotransmission systems. Thusly, the utilization of peptide radiopharmaceuticals could incredibly build the analytic capability of neuro imaging technology [108-111].

Ex: Potential candidates for neuro imaging include epidermal growth factor (EGF) peptide radiopharmaceuticals for the early detection of brain tumors and peptide radiopharmaceuticals as a diagnostic brain scan for Alzheimer disease.

- **Protein Neurotherapeutic Agent and Neuroprotection In Stroke**

All small-molecule neuroprotective agents have fizzled in clinical stroke trials in light of the fact that either (a) these molecules have unfavorable security profiles or (b) the drugs don't cross the BBB.

The restorative window for neuroprotection is the initial 3 hours after stroke, and amid this time, the BBB is in place. The BBB is upset in later stages taking after stroke, however right now, chances for neuroprotection have been lost. Along these lines, if powerful neuroprotective specialists for stroke are to be created, these molecules must have great wellbeing profiles and must have the capacity to cross the BBB [112-114].

Ex: A model neurotrophin, brain-derived neurotrophic factor (BDNF), was reformulated to enable BBB transport, and the BDNF chimeric peptide is neuroprotective following delayed intravenous administration.

### **Future Prospects of Brain Drug Delivery**

There are many technological challenges to be met, in developing the following techniques:

- Materials for nanoparticles those are biocompatible and biodegradable.
- Devices for recognizing changes in attractive or physical properties after particular tying of ligands on paramagnetic nanoparticles that can connect with the measure of ligand [115-116].
- Infection like systems for intracellular conveyance.
- Nanoparticles to enhance devices, for example, implantable devices /nanochips for nanoparticle discharge, or multi supply medicate conveyance chips
- Nano - drug conveyance systems that convey huge however exceedingly confined quantities of drugs to particular regions to be discharged in controlled ways
- Controllable release profiles, particularly for sensitive drugs
- Nanoparticles for tissue engineering; e.g. for the conveyance of cytokines to control cellular growth and separation, and stimulate recovery; or for covering implants with nanoparticles in biodegradable polymer layers for supported release.
- Easy to understand lab-on-a-chip devices for purpose of-consideration and disease prevention and control at home.
- Architectures/ structures, for example, biomimetic polymer, nanotubes.
- Progressed polymeric carriers for the conveyance of therapeutic peptide/proteins (biopharmaceutics), And additionally in the improvement of: Combined treatment and medical imaging, for instance, nanoparticles for determination and control amid surgery (e.g. Thermo-therapy with attractive particles). Cell and gene targeting systems.

## Recent patents

No.	Document	Document title
1	US20080235817	Artificial mammalian chromosome
2	US20080234377	Polyunsaturated fatty acids for treatment of dementia and pre-dementia related conditions
3	US20080234368	Therapeutic compositions and methods of use
4	US20080234356	2-phenyl-3,3,3-trifluoro-2-hydroxypropionic acid derivatives
5	US20080234313	Novel inhibitors
6	US20080234233	Medicament for treatment of neurodegenerative diseases
7	US20080234200	Method of treatment of a metabolic disease using intranasal administration of exendin peptide
8	US20080233132	Multiple sclerosis therapy

## CONCLUSION

Brain Targeting has got the consideration of the numerous analysts because of its application in different diseases identified with CNS. Just few drugs can infiltrate the BBB and enters the CNS, so different systems are created for drug conveyance. It rises that the nanotechnology and by utilizing different courses of drug administration like intra nasal procedure drug can infiltrate the BBB proficiently. Further the altered colloidal particles and different adjusted liposomes upgrade presentation of the BBB because of delayed blood dissemination, which supports cooperation and entrance into brain endothelial cells. This system has clinical advantages like lessened drug measurement, diminished symptoms, non-invasive routes, and more patient compliance. We still require developing a cost-effective system that can be used in various CNS disorders efficiently with minimum side effect.

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