



## Challenges and Strategies for Drug Transport across the Blood Brain Barrier

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**Abstract:** One of the most challenging fields for pharmaceutical and biotechnological products is the drug delivery to the central nervous system. According to the WHO records, 6.8 million people die every year with neurological disorders and the numbers are increasing every year. All the drug delivery strategies to the brain are restricted by the Blood-Brain Barrier (BBB) which limits the therapeutic drug from reaching the targeted site thus showing poor therapeutic effects. Therefore, the need for the development of new neurotherapeutics is important as the current treatment does not provide an effective solution to the BBB challenges. Several pharmacological, physiological and BBB temporary disruption strategies are currently under research to enhance the penetration of the drug across the BBB. The developments made using these strategies and associated challenges are discussed in detail.

**Keywords:** Blood Brain barrier, Drug transport, BBB disruption, Pharmacological modification, nanocarrier

### 1. INTRODUCTION

The epidemic data of common central nervous system (CNS) diseases such as stroke, neurodegeneration, brain tumors and multiple sclerosis is depressing and really there is a huge medical need for their treatment and management. According to the report of WHO, around 1.5 billion people globally are suffering from neurological diseases and out of which more than 50 million people are suffering from epilepsy and around 47 million are having dementia [1]. In addition, because of a normal life expectancy increment to nearly 70 years, around half of the population begins to experience symptoms of Alzheimer's Disease (AD) at this age which in turn may increase the incidences of developing AD from 11% to 14% by 2020[2]. Other than hereditary reasons or age and related reasons, the greater part of the degenerative CNS pathologies such as Creutzfeldt - Jakob's malady, Parkinson's illness (PD), AD, and Huntington's ailment, numerous sclerosis, and amyotrophic lateral sclerosis are creating as an outcome of wrong way of life. Expanded hazard factors such as liquor, medications, dietary mishandle in addition to stress are other causative factors. The emergency of developing CNS disease is

becoming particularly serious in developing countries because of a wide and uncontrolled spread of HIV infection as 75% of the patient eventually suffer from CNS diseases like encephalitis, CNS lymphoma, etc. However, the treatment therapies to the brain disorder is not sufficient and the reason behind is strict protective role of BBB which do not allow drug molecules to pass through and get in to the brain for therapeutic effect. Thus, there is a huge need to know the molecular mechanism of the disease, BBB barrier challenges and to develop such drug delivery system which can act as a potential treatment option for CNS diseases. Additionally, it is essential to know about BBB modifications usually take place in pathological condition in order to take advantage of these characters in developing a novel drug delivery system capable of efficaciously transporting the drug across the BBB and targeting damaged areas of the brain.

The BBB plays an important and protective role in controlling homeostasis of the brain as well as regulating movement of the molecules in and out of the brain. BBB's failure in doing so can lead to the interruption of the unique multicellular structure of the brain which at the end can lead to neurodegeneration, neuroinflammation as well

as lead development of brain diseases and disorders such as Parkinson's disease and Alzheimer's disease. On the other hand, this protective role of BBB is a big challenge for formulators for developing drug delivery systems which can cross the BBB and deliver drug into the brain. Thus, the most critical factor restricting the advancement of new medications for the CNS is the BBB. Major limitation with macromolecules such as pharmaceutical drugs, peptides, recombinant proteins, monoclonal antibodies and RNA obstruction (RNAi) based drugs is difficulty in crossing BBB [3]. There is a typical misconception that small particles promptly cross the BBB, however > 98 of every single little atom don't cross the BBB either [4]. Consequently, the pharmaceutical innovation commitment to this zone is of fundamental significance.

In this review, we have discussed composition and specific features of BBB and challenges in drug transport through the BBB. Additionally, the strategies applied so far to overcome the challenges in drug transport across the BBB with the most promising functional outcomes has also been discussed.

### 2. BLOOD-BRAIN BARRIER AND ASSOCIATED CHALLENGES FOR DRUG TRANSPORT

It is a unique and important boundary between circulating blood and neural tissue is BBB which only allows oxygen and nutrients to pass across and get into the brain. BBB is mainly made up tightly interconnected endothelial cell of brain and pericytes is present in a discontinuous layer throughout the BBB. Initiation of revascularization to maintain the integrity of BBB is the unique characteristic property of cerebral endothelial cells to restrict trans endothelial transport [5]. Presence of specific proteins such as tight junctions (TJs) and adherens junctions (AJs) are responsible for strong cohesiveness of endothelial cells throughout the barrier. As endothelial cells are encompassed by a basal lamina, collagen and heparin sulfate, they can be intriguing targets for the drug transport.

This barrier is responsible for its very low permeability which limits the drugs from entering and in turn obstructing the therapeutic effects in the central nervous system. There are mainly three basic pathways of molecule transport across the BBB. First is paracellular route in which small ions and solutes can pass through BBB from the space in between the endothelial cells based on their concentration

gradient. Second pathway is transcellular in which certain lipid soluble nonpolar small drug molecules may cross the BBB by means of lipid-interceded diffusion process, giving the drug an atomic weight of lower than 400Da and structures under 8 to 10 hydrogen bonds. The third one is receptor mediated transcellular passing in which the molecule binds to specific receptor present on BBB such as GLUT-1, transferrin and can cross the BBB [6]. However, these properties are inadequate in most small molecular drugs and all substantial drug particles consequently ended up being more intrusive and do not have accurate specificity of targeting. Another challenge is presence of efflux proteins such as P-glycoprotein, ATP binding cassette (ABC) transport proteins, Multidrug Resistance Protein-1 (MRP-1) which may actively exclude out the drug from the brain [7].

### 3. STRATEGIES TO OVERCOME CHALLENGES OF THE BLOOD-BRAIN BARRIER

Drug delivery to the central nervous system is one of the challenging area for the delivery of the pharmaceutical products. This is mainly because of the tight junction of the highly polarized endothelial cells of the BBB. A few unique methodologies for conveying atoms over the barrier have been created for treating neurodegenerative diseases, and can be extensively categorized by intrusive, pharmacological, and physiological approaches [8].

#### 3.1. Intrusive Strategy

This strategy includes disruption of BBB. The intrusive strategy depends on delivering the drug molecule into the cerebrum tissue through fluctuating strategies, for example, the utilization of polymers or microchip systems and transient disturbance of the BBB. Conventionally, the temporary disruption of the BBB take place when a hyperosmolar mannitol solutions is infused intra- arterially or by co-administrating the bradykinin agonist RMP-7 which leads to dehydration and shrinkage of the endothelial cells with a consequential opening and widening of the tight junctions. Another method is mechanical disruption of BBB to deliver a high payload of drug locally in the brain while minimizing the level of drug in systemic circulation resulting in efficient treatment therapy and reduced side effects. However disadvantages associated with this strategy is, these methodologies are invasive, prompting dangers of contamination and CNS

infection, causes rapid clearance of drugs from brain tissue and imparts toxicity and harm to cerebrum tissue [9], [10].

### 3.2. Pharmacological Strategies

It is also known as pharmacological drug modification approach for transporting drug through BBB. Drug modification may be done by chemically modifying a pharmaceutical active drug to form its active prodrug which can enhance its BBB permeation. Another approach depended on the significant improvement of lipophilic nature of drug and enabling them to diffuse effectively through the BBB. Formation more lipophilic prodrug or increased lipophilicity of drug molecule may improve its transport across the BBB but at the same time also enhances its metabolism and active clearance by efflux proteins which are drawbacks of this strategy [11].

### 3.3. Physiological Strategies

Linking the drug molecule to a carrier is also frequently employed to enhance lipophilicity of drug and as a non-invasive tactic for crossing the BBB [12]. However, combining drugs that satisfy this condition take out countless valuable polar particles that could be utilized to treat CNS issue [13], [14], [11], [15], [16]. A second plausibility is to utilize little hydrophilic drugs to encourage traversal of the BBB by the paracellular hydrophilic dissemination pathways; however most of the molecules are can only enter the inter-endothelial space of the cerebral vasculature up to the tight intersections, and not beyond.

The physiological method has the advantage of the transcytosis limitations of transporting receptors communicated at the BBB surface with a specific end goal to infiltrate the obstruction[17]. Another technique comprises in the utilization of receptor-intervened endocytosis by conjugation of medication particles to ligands, for example, antibodies and peptides, against receptors that are communicated on the surface of endothelial cells of the barrier, enabling the medication to be transported into the cerebrum [18],[19]. A physiological approach of modification of drug molecules include conjugation of drug to ligand moiety such as antibodies, lectins, sugar and transferrin protein which can utilize the normal endogenous BBB nutrient transport pathway for drug transport [12]. This approach is importance as here the system is guided through a specific ligand or a unique antigen to target specific

receptors on the surfaces of the cell and thus it can trigger receptor-mediated transcytosis for enhanced delivery of drug cargo molecule across the BBB[20]. The insulin receptor, LDL receptor and its related protein and transferrin receptor are some of the important receptors present on BBB and have been widely explored [21],[22],[23, 24]. However, the disadvantages for this approach are that ligands have low rate of drug dissociation.

For transporter-mediated delivery, that utilized by peptides and small molecule nutrients, the drug should mimic the carrier substrates to be transported, hence this approach necessitates careful consideration of the kinetics available to transport physiologic molecules, the structural binding requirements of the transporter and the appropriate drug modification that allows binding and transport without loss of activity in-vivo [25].

The other similar approach is adsorptive mediated endocytosis which in contrast to receptor-mediated transcytosis, involve endocytosis in vesicles of charged substances without a specific mechanism [26]. Cationic peptides and proteins with a basic isoelectric point bind to the luminal plasma membrane via electrostatic interactions with anionic sites, subsequently adsorptive endocytosis is initiated. It was demonstrated that protein transduction domains (PTDs), TAT and polyarginines enhance brain uptake and bypass the P-gp efflux of some anti cancer and peptide drugs.

Lastly, the nanocarrier approach explored in drug transport to CNS and targeting include development of various nanoscale drug delivery systems such as micelles, liposomes and nanoparticles[27], [28], [29]. The advantages here is a nanocarrier can load both the hydrophilic as well as a lipophilic drug, it can load a large amount of drug, its surface modification helps in improving their permeation across the BBB and site specific drug delivery. It can be considered as a most important strategy as it also protects drug from enzymatic degradation, there is reduced side effects and can also transport non-transferable molecules [2]. However, at the time of designing and developing of nanocarriers, their fate after intravenous administration including biodistribution following opsonisation should also be considered by developing stealth or PEGylated nanocarrier system to improve its circulation time[30].The olfactory pathway has

also been explored wildly in recent times. It is noninvasive method of targeting a drug to the brain.

### 4. CONCLUSION

To conclude, the huge need and chief concern regarding drug transport across the BBB and drug delivery to the brain has initiated research that focuses on physiological and biopharmaceutical challenges that prevent drug access and recognize the strategies in rational drug and delivery system design. All three of these methodologies discussed here have certain challenges that limits its potential application in treating neurological illnesses. The deficiency in techniques to transport drugs across the BBB leads to extensive efforts into the utilization of nanotechnology to deliver drugs successfully over the BBB without modifying their impact is being researched. For this reason, nanoparticles with various sizes, models, and surface properties have been designed for CNS drug delivery. The knowledge gained is transforming the approach to drug-targeting and prodrug research. The amalgamation of this research into early drug discovery to expand the chemical space of CNS-likeness drug molecules is highly appreciated. Thus more interdisciplinary and collaborative research in the field can guide innovative utilization of new strategies to solve the drug delivery problem in order to develop potential treatment therapies for CNS diseases.

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