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REVIEW ON ROLE OF BBB AND ITS TRANSPORT MECHANISMS IN THE DEVELOPMENT OF BRAIN TARGETED DRUG DELIVERY SYSTEMS

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ABSTRACT

The development of brain drug delivery system which can effectively administer drug into brain region has been very challenging for formulation scientists. The presence of highly selective blood brain barrier and tight junction of epithelial cell make the permeation of most drugs difficult. Many researchers have tried to utilize traditional approaches like prodrugs and temporary reversible disruption of blood brain barrier but they are not much effective. Recently the development in the field of nanotechnology has shown some promising results in terms of development of proper brain targeted drug delivery systems. The thorough understanding of underlying mechanism by which some substances are crossing BBB is very important to develop an effective brain targeted drug delivery system. In this review the focus of discussion is on the understanding of various mechanism and effective exploitations of valuable promising leads by which a drug can transport across the BBB to enter into the CNS.

KEYWORDS: Brain drug delivery system.

INTRODUCTION

The development of an effective central nervous system (CNS) drug delivery system has been a long time challenge for formulation scientists and pharmaceutical companies across the globe. The main reason for this is the highly selective nature of Blood brain barrier (BBB). It has been reported that almost 98% of drugs coming out from the research and development stage and which are having CNS activity, fail to cross the BBB and to achieve minimum therapeutic concentration. This phenomenon of low permeability across BBB is not only limited to large molecules but more than 98% small molecules also have similar permeability issue. The effective solution of this problem would lead to a great opportunity to treat many CNS disorders more precisely. Researchers have tried many traditional approaches to achieve therapeutic goal in case of CNS drug delivery. Few such approaches are prodrug, reversible disruption of BBB, intracerebral injection and CNS implants.[1]

The prodrug concept mainly explained by the chemical or enzymatic biotransformation to an active drug from the bioreversible derivatives of drug molecules. This concept is helpful in many instances where a direct permeation of a drug is limited to any particular tissue or organ. In case of CNS drug delivery this concept is used to improve the lipophilicity of the drug molecule and thereby increasing the permeation of drug molecule through predominantly lipophilic BBB. A detailed study of prodrug based on lipophilic chemical derivatives i.e. lipophilic esters and various hydrophobic compounds suggested the limited use of this approach to enhance drug permeation through BBB. The recent advancement on prodrug based CNS drug delivery includes receptor mediated prodrug transport, carrier mediated prodrug transport and gene mediated enzyme prodrug therapy. The major limitation in the success of prodrug approach is the premature conversion of prodrug in to active drug molecule without reaching to the actual site of action i.e. enzymatic conversion in plasma.

One more traditional approach for the improvement of permeation of drugs is to cause reversible disruption of the BBB. Such reversible disruption of BBB makes the tight junction of the endothelial cells leaky and allows access to substances to the brain. Various techniques such as osmotic disruption, ultrasound disruption and disruption by bradykinin analogue have been studied by many researchers. In case of osmotic disruption method the shrinkage of endothelial cells due to osmotic shock causes the disruption of the tight junction. The preadministration of a hypertonic mannitol solution followed by the administration of drug through intra caroitid artery is one such example of osmotic disruption. This approach has shown higher concentration of drug into brain and in tumor tissues as compare to only drug administration.[2]

Application of MRI guided focused ultrasound technique is also useful for developing brain drug delivery system.

A study shows that the repeated sonication caused enhanced extravasation of Evans Blue. The sonication was done at an ultrasound frequency of 1 MHZ and a repetition frequency of 1 HZ. In comparison to a grup with single sonication, two fold EB extravastion was observed in a group with double sonication. Even the overall EB extravasation was more in both single and double sonication groups as compare to group without sonication. In one such stydy it has been reported that the selective bradykinin receptor agonist, Cereport which is also known as RMP-7 can increase the permeability of many drugs through the BBB. Drugs like carboplatin, loperamide and cyclosporine – A have shown enhanced permeation when coupled with cereport (RMP-7). The major disadvantage of BBB disruption approach is that there is an increased uptake of plasma albumin and other protein components of blood in brain which are known to be toxic to brain cells.[3]

Other approaches like placement of implants and the intra cerebral injection are also useful for improving the permeability in case of CNS drug delivery system. Both approaches work on the basic principle of diffusion to drive the drug into brain. Researchers have prepared and evaluated various types of paclitaxel loaded lipid implants and PLGA- based microparticles with controlled release kinetics ranging from several days to weeks. Knowing the fact that paclitaxel upon the systemic administration cannot cross the BBB these microparticles are directly administered in to brain tissue by intracranial administration. This approach has shown positive response in terms of the local treatment of operable and inoperable brain tumors.

Inspite of small successes all these traditional approaches have failed to deliver drug effectively and efficiently to the brain. In addition to this there are many adverse effects associated with these traditional approaches such as the highly destructive nature of some approaches can lead to the long term permanent damage to specific tissue of organ. This leads to the need for the development of novel brain targeted drug delivery systems which can deliver drug to brain effectively with no or fewer side effects to the patient.[4,5]

Approaches for brain targeted drug delivery:[3]

A. Invasive

- Intracerebroventricular (ICV) infusion
- Convection-enhanced delivery (CED)
- Intra-cerebral injection or implants
- Disruption of the BBB.

B. Non-invasive

- Chemical techniques

a. Prodrug

- Colloidal Techniques

a. Nanoparticles

b. Liposomes

C. Miscellaneous techniques

a. Intranasal delivery

Structure of BBB

The main role of BBB is to control the exchanges between different compartments of blood and brain. It is a dynamic and complex barrier which separates blood from central nervous system. It gives protection by prohibiting the entry of harmful substances such as toxic molecules, pathogens and various external molecules and helps in to maintaining brain homeostatis. The endothelial cells of BBB are quite different from cells present in other body parts. The presence of intracellular tight junction reduces paracellular diffusion of hydrophilic molecules. The BBB also possesses high number of mitochondrial cells and thereby it has got high metabolic activity and relatively higher number of active transporters. The basal lamina is composed of collagen, glycoproteins and proteoglycans. The basal lamina is responcible for the dynamic regulation of BBB along with multiple basal lamina proteins, matrix metalloproteases. The glial delivered neurotrophic factors, angiotensin-1 and angiotensin-2 along with astrocytes are responcible for the integrity of BBB. The barrier capacity of BBB can be decided by considering pericytes to endothelial cells ratio in brain.[6,7]

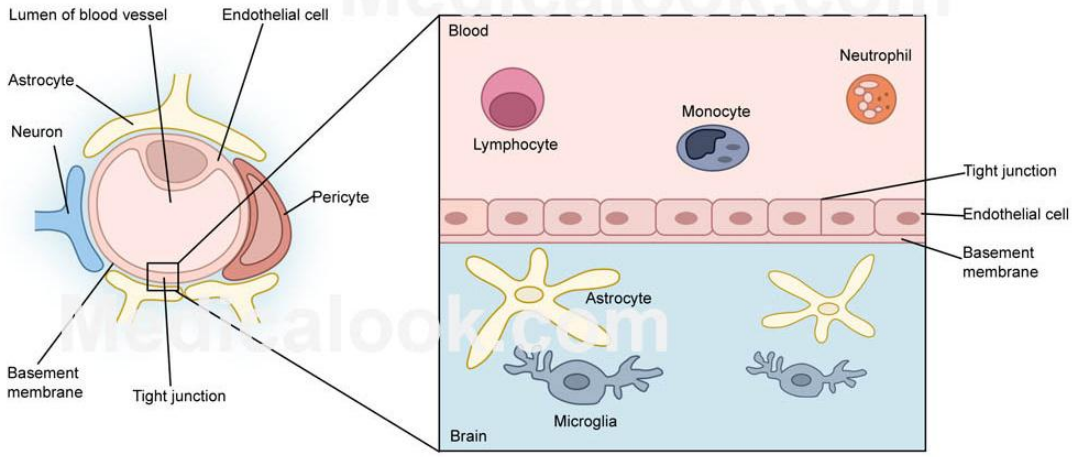

Figure 1: Structure of BBB.

Features of the BBB

The plasma ultra-filtrate formation in the central nervous system is prevented by three major modifications to the capillary bed of the brain. The rate of pinocytosis is greatly affected by the tight junctions who held together brain endothelial cells. Such modifications are needed to regulate leakage of serum proteins into the central nervous systems under normal condition. It has been observed that in such condition too many substances can cross the vascular BBB by different mechanisms. Examples of such mechanisms are (I) Transmembrane diffusion (II) Saturable transport (III) Adsorptive endocytosis and (IV) Extracellular pathways.[8]

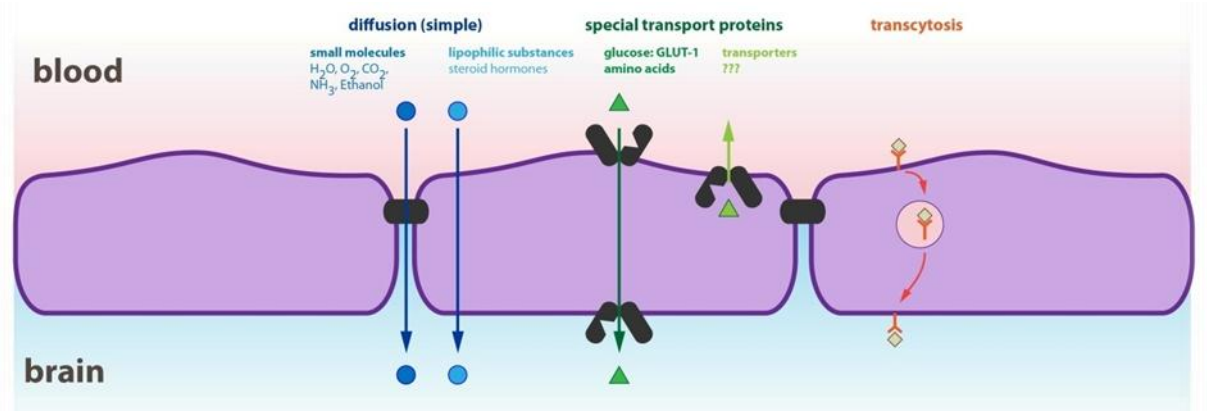

Figure 2: Routes for drug permeation across BBB.

Transmembrane diffusion

Majority drugs cross the BBB by trnasmembrane diffusion. This mechanisam is non saturable in nature and depends on drug melding into cell membrane. Drugs with low molecular weight and high degree of lipid solubility are more likely to cross BBB by trnasmembrane diffusion. After the crossing of BBB via this mechanism, drug has to partition into the aqueous environment of the brain interstitial fluid to exert and effect. Due to this thing highly lipid soluble drugs are more likely to get sequestered by the blood capillary bed and do not reach to brain cells after crossing BBB. However the lipid solubility of drug results into high uptake by the peripheral tissue on brain and lowers the concentration of drug into blood. Thus the lipid solubility which increases the rate of transport across BBB at the same time lowers the amount of drug presented to brain. The success on any brain targeted drug delivery system is decided by both the rate of drug transport across BBB and the amount of drug presented to the brain. It is necessary to find a balanced approach between rate of penetration and concentration of drug in brain, while using higher lipid solubility technique for enhanced penetration of drug across BBB. Various factors like charge, tertiary structure and degree of protein binding affects the penetration of drugs across BBB. The molecular weight of drug also plays very important role in determining the rate and amount of drug penetration across BBB. In case of the influence of molecular size of drug on the BBB penetration is stated by the fact that the rate of penetration across BBB is inversely proportional to the square root of molecular weight of drug. Many researchers have reported that drugs in the range of 400 to 600 Da molecular weight are more likely to cross BBB. Many researchers have applied Lipinsky's rule of 5 to screen out drugs and found that few drugs with molecular weight more than 500 Da can also cross BBB. On the other hand a study carried out by Levin on 27 drugs showed that 4 out of 27 drugs with molecular weight over 400 Da have not shown any satisfactory result in terms of brain uptake. Later it was observed that these substances are substrates of P-glycoprotein, a major brain to blood or efflux pump located on the BBB to prevent large number of small, lipid soluble molecules from entering the CNS. Several peptides and proteins with molecular weight more than 600 Da have been known to cross the BBB in quantity sufficient to produce therapeutic effect inside CNS. Delta sleep inducing peptide and enkephalin analogs are examples of such peptides and proteins. Cytokine-induced neutrophil chemoattractant-1 is the largest molecule with molecular weight of 7800 Da which has penetrated across BBB till date. Brain-to-blood efflux by P-glycoprotein can greatly limit the rate of uptake by the BBB and is a major obstacle in drug development. The pharmacogenomics of P-glycoprotein show that about 30% of the population overexpress it and so are less sensitive to the CNS effects of its ligands, while about 25% of the population underexpresses it. Such individual variation has been linked to sensitivity to drugs for the treatment of AIDS and epilepsy.[9,10]

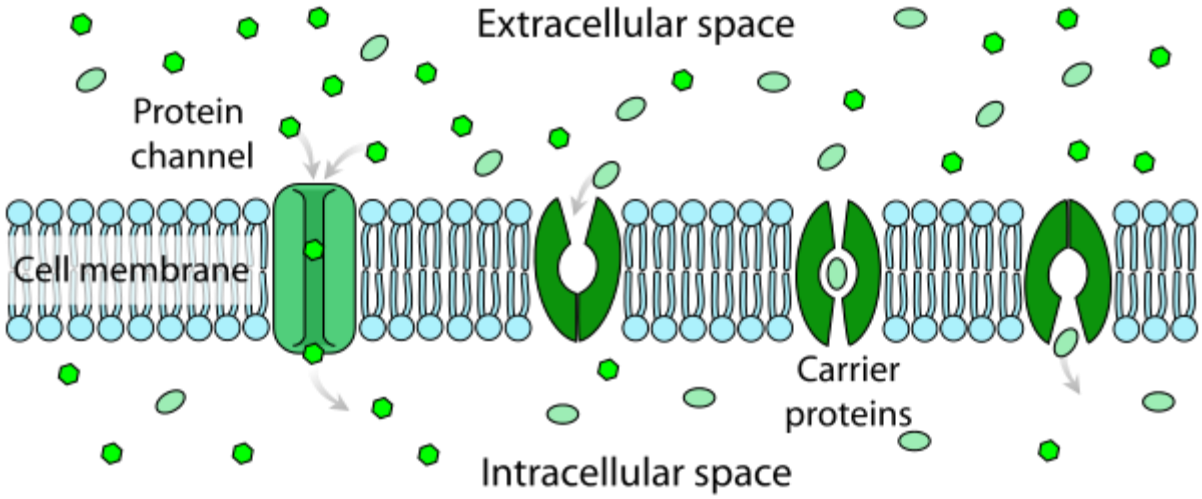

Figure 3: Drug permeation across BBB by transmembrane diffusion.

Saturable transport systems

Apart from transmenbrane diffusion many drug or drug like molecules have been reported to cross BBB by saturable transport systems. Few such examples are L-DOPA, caffeine, vitamin B12 and vitamin B6. About 10 times more amount of endogeneous ligand or a transporter is possible to cross BBB by this mechanism compare to transmembrane diffusion. In addition to this many transporters for regulatory molecules such as peptides and proteins are taken up readily by specific regions of brain when administered by this mechanism. Thus the utilization of saturable transport mechanism and transporters is hugely beneficial for the development of brain targeted drug delivery systems even for water soluble drugs.[11,12] The intake of drug is comparatively low in case of efflux transport than in case of influx transport. The BBB possesses many other efflux transporters like p-glycoprotein. It has been observed that the rate of ligand transport in saturable system is well regulated across the BBB. In case of flow dependent substances like glucose transport rate across BBB is mainly governed by cerebral blood flow. Various agents have been reported to alter and regulate rate of transport of specific substances. The regulated transport rate of peptide transport system-1 by leucine and epinephrine regulated transport of leptin, ghrelin and insulin are examples of such agents. Under specific physiological conditions the BBB transporters adapt to serve the needs of the CNS. The system gets disturbed by the uncoupling of BBB functions and CNS need in a diseased condition such as obesity can lead to the decreased leptin transport due to the development of peripheral leptin resistance. In Alzheimer disease a decreased efflux of amyloid beta protein has been reported by researchers.[13,14]

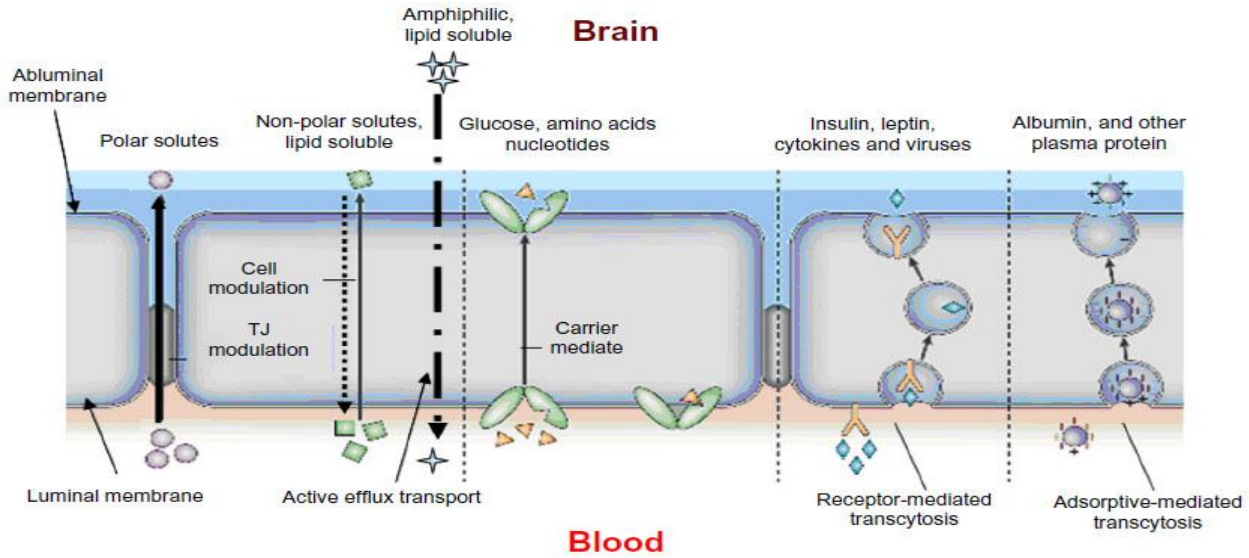

Figure 4: Drug transport across BBB by saturable transport system.

General strategies for drug transport

Many researchers have been focusing on the development of brain targeted drug delivery systems by considering in silico analysis and high throughput screening. These type of efforts are restricting drug discovery to substances that are crossing BBB by

transmembrane diffusion. It has been observed that in silico method is comparatively less efficient in the search of CNS drug candidates than in the search for drug candidates absorbed by the gastrointestinal tract. This is mainly because of factors such as cerebral blood flow, influx and efflux transporters, protein binding in the blood, clearance from blood, sequestration by BBB tissues, and enzymatic activity by peripheral tissues, blood, the CNS and at the BBB can modify or override transmembrane diffusion. Most popular approach to the drug development for the brain targeting is to harness transporters. Approach like trojan horse strategy is more usual than others. In this approach a reversible complexation or attachment of drug with an agent that can cross BBB easily happens. Such reversible coupling can also improve peripheral pharmacokinetics. However the hybrid complex of drug and carrier is often not recognized by the original transporter or the hybrid complex gets diverted to lysosomes for destruction. Some hybrid complexes may utilize other vesicular pathways across BBB to enter into CNS. Overall the poor understanding of cell biology of BBB vesicular system is affecting negatively to the effective utilization of promising leads for the development of brain targeted drug delivery systems.[15,16] There is not much progress in the direction of the development of analogs of transported ligands. Many endogenous substances that could be the basis of CNS drugs, such as the feeding hormones and cytokines, are transported across the BBB [30] However, the limited peripheral pharmacokinetics of such endogenous compounds makes them less likely to be used for the drug transport across BBB. These analogs have to retain their affinity for the BBB transporters and for the CNS receptor and at the same time they have to deal with peripheral enzymes and clearance mechanisms. When disease states affect the BBB or the BBB is itself impaired, then it becomes a therapeutic target in its own right. A classic example is multiple sclerosis in which the BBB becomes leaky and allows the entry of immune cells into the CNS. However, the passage of immune cells across the BBB is a highly regulated process and the leakage is likely a byproduct of immune cell trafficking and not the other way round. Certainly, the luminal surface of the capillary bed does not require passage across the BBB and, hence, drug strategies used to target peripheral tissues are applicable to this half of the BBB. Luminal receptors are capable to induce brain endothelial cells to secrete substances such as prostaglandins, cytokines and nitric oxide into the CNS can also be targeted. This suggests that the BBB itself could be used as the source of CNS 'drugs'. 'Bypassing' the BBB can also be an effective strategy, especially for selected cases or situations. For example, intrathecal administration for delivery of drug to the brain is ineffectual for small, lipid soluble drugs. However, this route may be an option for large regulatory proteins with negligible brain-to-blood efflux. Intranasal delivery of drugs, including peptides, shows a great deal of promise. Nasal delivery of insulin, for example, has had positive effects in treating Alzheimer's disease.[17,18]

Examples and special cases

Many researchers have been succeeded to some extent in order to develop an effective drug delivery system for the CNS. It very important to understand the underlying mechanisms and promising leads by which some substances are crossing BBB to enter into the CNS. One should also consider the thorough understanding of peripheral pharmacokinetics of drugs to make them cross BBB effectively. However there is a huge gap between the present understanding of the BBB and the complete understanding of it. One such example is that there still is a scope of discovering more number of BBB transporters. Recently discovered two new transporters are more likely to be useful for researchers to make progress in the development of brain targeted drug delivery system. Antisense molecules have been assumed to be incapable of crossing the BBB.[19] The rapid clearance of any mRNA material in the circulation would certainly justify this assumption. However, enzymatically resistant analogs such as peptide nucleic acids and phosphorothioate oligonucleotides (PONs) can cross the BBB in sufficient amounts to affect CNS function. The PONs are transported across the BBB by a saturable transport system. This transporter has been used to deliver an antisense molecule directed against amyloid precursor protein, which effectively reverses the cognitive deficit in an animal model of Alzheimer's disease. PONs have also been directed at the efflux transporter of PACAP27. The PONs reduce expression of the transporter, increase PACAP27 retention by brain after its peripheral administration, and improve outcomes in animal models of stroke and Alzheimer's disease. These results show that targeting efflux systems at the BBB with antisense molecules can improve drug delivery to the brain. Mucopolysaccharidoses consist of a number of diseases in which missing enzymes lead to the accumulation of glycosaminoglycans in brain and peripheral tissues. Enzyme replacement clears the glycosaminoglycans from the peripheral tissues, but not from the CNS as the enzymes do not cross the BBB. However, it was recently discovered that the mannose-6 phosphate receptor acts as a saturable transporter at the neonatal BBB. As a result, enzyme given to the neonate is effective in clearance of glycosaminoglycans from the CNS. Unfortunately this transport function is lost with development. Recent work has shown that transporter function can be re-induced in the adult with epinephrine. How epinephrine invokes this re-induction of activity is unclear, but it may be a useful strategy for delivery of enzyme to the CNS.[20]

CONCLUSION

The BBB is a complex barrier regulating the entry of substances into the CNS. It possesses barrier, secretory, enzymatic and transporter activities which regulates the entry to substances into the CNS. Researchers are exploting possibilities to develop an effective brain drug

delivery system based on mechanism such as Transmembrane diffusion, harnessing of transporters, adsorptive endocytosis, and extracellular pathways by which any substance can cross the BBB and enter into the CNS. Unfortunately, our understanding of the BBB in many areas, especially those of saturable transport systems and vesicular pathways, is limited. Future successes in CNS drug discovery will likely result from an interplay of exploratory research and rational drug development.

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