

NEUROSURGICAL STRATEGY FOR DRUG DELIVERY TO BRAIN

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ABSTRACT

Drug targeting to the brain could be achieved by going either "through" or "behind" the BBB. Drug delivery to brain requires advances in both, drug delivery technologies and drug discovery. Delivery of a pharmaceutical agent to the systemic circulation, and consequently to the site of action to produce a desired pharmacological effect, is the ultimate goal of drug delivery. Any drug, delivered by any route, will have to encounter barriers before reaching at the site of action. There are three general approaches for increasing brain penetration of drugs. First is to circumvent the difficulties associated with drug permeability in the BBB and/or BCSFB by direct central administration of drug into the brain. Second approach is to temporarily break down the BBB. The third approach is to use chemical modifications of the drug.

Keywords: BBB, cellular barriers, BBB disruption, Delivery routes in the BBB.

INTRODUCTION

What Juliano said "The practitioners of drug delivery research find themselves in difficult, however, interesting situation of being at a nexus between an ever growing stream of information about drug and biological system, and ever expanding plethora of demands for more sophisticated therapeutic system."¹ Essential aspect which should be considered for the designing of delivery system to achieve goal include target, carrier, ligand(s) and physically modulated components. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preidentified target in the therapeutic concentration, while restricting its access to non-target normal cellular linings, thus minimizing toxic effects and maximizing therapeutic index.

CELLULAR BARRIERS TO THE DRUG DELIVERY IN THE CNS

There are two cellular barriers that separate the brain extracellular fluid from the blood. The first and largest interface is the brain capillary endothelial cells that form the BBB (Fig 1 & 2). The brain capillaries are a continuous layer of endothelial cells connected by well developed tight junctional complexes² that is why passive diffusion of drugs and solutes between the endothelial cells is restricted. They lack fenestrations and have reduced pinocytotic activity. These characteristics further restrict the

movement of compounds from the blood into the brain.³ The presence of tight junctions between the brain capillary endothelial cells means that the paracellular pathway for drug delivery is highly restricted. Lipid soluble drugs with a molecular mass less than 600 can pass through the BBB via passive diffusion through the brain endothelial cells. Factors that influence passive diffusion include molecular volume, charge, and the hydrogen bonding potential of a compound.⁴ Besides the diffusional pathway, compounds can move across the BBB through the vesicular transport and via specific transport or carrier systems within the brain endothelial cells.

The second barrier is the blood-cerebrospinal fluid barrier (BCSFB). It is composite barrier made of the choroid plexuses⁵ and the arachnoid membranes. The epithelial cells in the choroid plexus that form the BCSFB have complex tight junctions and these tight junctions are more permeable than those found in the endothelial cells of the BBB.⁶ Blood-cerebral spinal fluid barrier properties are provided by tight junctions formed between the choroid epithelial cells. Choroid endothelial cells are fenestrated. Although the apical membrane of the epithelial cells forming the BCSFB has numerous microvilli, the total surface area is smaller than the BBB.

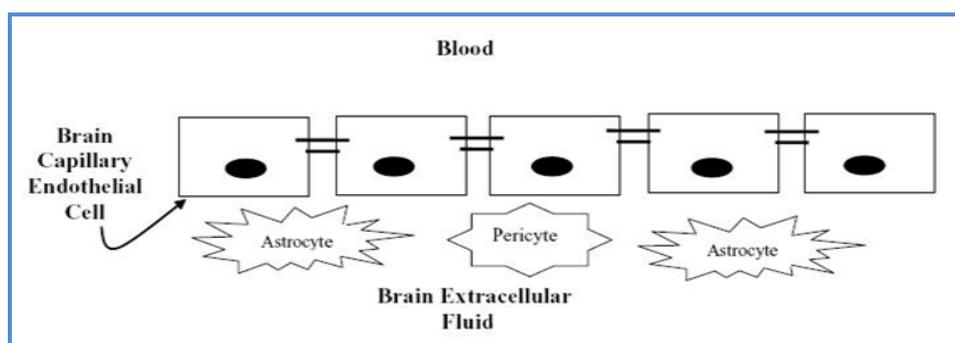


Figure 1: Blood-Brain Barrier

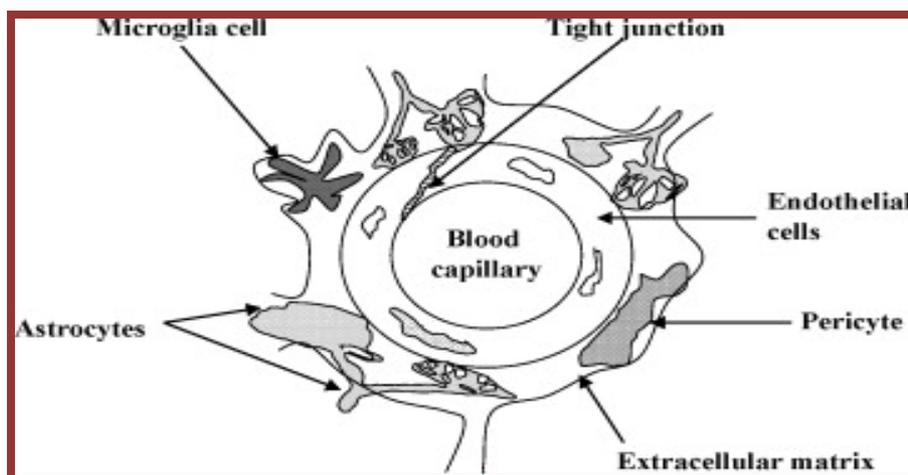


Figure 2: Schematic representation of the brain capillary endothelium that form the blood–brain barrier (BBB).

Characteristics of Blood Brain Barrier

Blood-brain barrier

Non-fenestrated endothelia

Circumferential belts of tight junctional complexes

Secondary liposome's containing acid hydrolases

Extralysosomal hydrolytic enzymes (e.g. monoamine oxidase)

Blood-CSF barrier

Choroid plexus epithelium

Circumference belts of tight junctional complexes

Secondary lysosomes containing acid hydrolases

Arachnoid matter

Circumferential belts of tight junctional complexes

STRATEGIES FOR BRAIN DELIVERY OF DRUG

Direct administration of drug to the brain

Intracerebral administration

This approach is invasive, requiring a craniotomy in which small hole is drilled in the head for intracerebroventricular (ICV) or intracerebral (IC) drug administration into the brain. The disadvantage of direct administration of drug to the brain is related to the limited brain distribution of the drug. This is illustrated in the studies by Krewson⁸ and co-workers, in which polymer implant containing radiolabeled nerve growth factor were placed in the rat brain and diffusion of factor monitored by autoradiography. In this, diffusion of nerve growth from polymer implant was limited to 2-3 nm. Limited CNS distribution was also observed following one-time bolus (ICV) injections of brain derived neurotropic factor in rat.⁹

Intrathecal Administration

Intrathecal administration is a means of circumventing the BBB delivery problems associated with large macromolecules such as proteins and peptides. Intrathecal administration involves the injection or infusion of drugs into the cerebrospinal fluid (CSF) that surrounds the spinal cord. The agents commonly administered by the intrathecal route for pain management are small lipophilic molecules. Proteins administered intrathecally have a much slower clearance from the CSF.¹⁰ The intrathecal route of administration is viable strategy for delivering large molecular weight macromolecular with limited lipophilic properties.

Nasal Administration

Another delivery option for bypassing BBB is through intranasal administration. Compared to intrathecal and intracerebral administration, IN administration is noninvasive means of delivery of therapeutic agents to the CNS.^{11,12} Because of unique connection between the nose and brain, the olfactory neural pathway provides the route of delivery for various compounds into the CNS. This pathway can also be used for delivery of various into the CNS. Small molecules such as cocaine and cephalexin can be transported directly to the CNS from the nasal cavity.¹³ Cephalexin preferentially entered the CSF after nasal administration compared to intravenous (IV) and intraduodenal administration in rats. The level of Cephalexin in CSF was 166-fold higher 15 minutes after nasal administration than those of the two routes.

In addition to small molecules, a number of protein therapeutics agents, such as neurotrophic¹⁴ factors and insulin,¹⁵ have been successfully delivered to the CNS using IN delivery.

Advantages

IN administration is a promising approach for rapid-onset delivery of medicaments to the CNS by passing the BBB. It improves the bioavailability of many presystemically metabolized drugs entering CNS, eliminating the need for systemic delivery and reducing unwanted systemic side

effects. It is also rapid and noninvasive. IN delivery does not require any modification of the therapeutics drugs and does not require the drugs to be coupled to any carriers.

However, there are also limitations. One of the limitations is insufficient drug absorption through the nasal mucosa. Many drug candidates cannot be developed for the nasal route because they are not absorbed well enough to produce therapeutic effects.¹⁶ Another constraints concerning nasal administration is that a small administration volume is required, beyond which the formulation will be drained out into the pharynx and swallowed.¹⁷

BBB disruption

The complex tight junctions that form between the brains capillary endothelial cells restrict the paracellular diffusion of molecules and solutes in the BBB. Modification of the tight junctions, causing controlled and transient increases in the permeability properties of the brain capillaries, is another strategy that has been used to increase drug delivery to the brain. Methods for disrupting BBB integrity through the breakdown of tight junctions include the systemic administration of hyperosmotic solutions,¹⁸ vasoactive compounds such as bradykinin and related analogs,¹⁹ and various alkylglycerol.²⁰

Osmotic agents

A Hypertonic solution of an inert sugar, such as mannitol or arabinose, ranging from 1.4 to 1.8 m, is delivered into the cerebral circulation through bolus injection or short-term infusion into the carotid artery.²¹ The cellular mechanism behind osmotic disruption of the BBB involves the physical pulling apart/breaking of tight junctions due to the shrinkage of cerebral endothelial cells and expansion of the blood volume caused by addition of the hyperosmotic agent. The BBB resumes its normal barrier functions within hours of returning the osmolarity of the blood to normal.²¹ During this period when the tight cellular junctions between the brain capillary endothelial cells have been compromised, paracellular diffusion of water-soluble drug and solutes into the brain is enhanced. Increases in both small-and large-molecule delivery take place and the subsequent return of the barrier function following osmotic disruption appears to be variable.

Osmotic disruption of the BBB has been used to increase the delivery of chemotherapeutic agents to the brain in the treatment of CNS tumours in rats.²²

Bradykinin analogs

Several endogenous vasoactive agents, such as bradykinin, histamine, nitric oxide, and various leukotrienes, to induce increases in BBB permeability in a concentration- and time-dependant manner. Many of these endogenous agents have narrow therapeutic windows and dose-limited side effects. Thus, although

capable of producing increases in BBB permeability, these endogenous agents have been proven difficult to apply safely for CNS drug delivery.

To circumvent the problems associated with the use of endogenous vasoactive agents, investigators have explored the use of structurally modified analogs. The best example of this is bradykinin analog labradimil (Cereport).The permeability increases observed with Cereport were greater in the area in and around the brain tumour compared to nontumor regions of the brain.

Alkylglycerols

A relatively new approach for transient disruption of the BBB involves the systemic administration of various alkylglycerols. There is reversible and concentration-dependant increase in BBB permeability to several anticancer and antibiotic agents. The extent of BBB disruption varied from a 2-fold to a 200 fold increase in methotrexate, depending on the length of the alkyl group and the number of glycerols present in the structure. The effects of alkylglycerols on large-macromolecule permeability in isolated brain capillaries is due to increases in permeability are which result from temporary breakdown of the tight junctions between the cells. The use of alkylglycerol to increase BBB permeability of anticancer agents has been examined in a rat glioma tumour model.^{23,24}

TRANSCELLULAR DELIVERY ROUTES IN THE BBB

Aside from either circumventing the BBB completely through central administration of a drug or reversibly opening the BBB, increased delivery of therapeutic agents to the brain can be accomplished through improved transcellular migration. The transcellular routes available in brain capillary endothelial cells include passive diffusion, specific transport systems, and endocytic processes present in the brain microvasculature.

Passive diffusion

Key factors influencing the passive diffusion of the drugs across the BBB are lipid solubility and molecular size. The relationship is described by the equation $D = \log P/MS^{1/2}$, where D is Diffusiion, $\log P$ is lipophilicity, and MS is molecular size. Thus, improving the passive diffusion of drug across the BBB can be accomplished by either increasing lipophilicity or reducing molecular size. As lipophilicity is dependent on polarity and ionization, modification and/or masking of functional groups on drugs provide a method for improving passive diffusion across the BBB. One of the method employed for increasing the lipophilicity of a drug is a creation of a prodrug. In this approach, water-soluble compounds with polar functional groups such as acids or amides, are chemically modified to create derivatives with increased lipid-solubility. The most common prodrugs are esters, since by appropriate esterification of molecules containing carboxylic, hydroxyl, or thiol functional groups, it is feasible to obtain derivatives with almost any desired lipophilicity or hydrophilicity.²⁵



Inwardly directed transport system in the BBB

To meet the metabolic needs of the brain, the endothelial cells that form the BBB express much selective carrier/transport system for delivering essentials nutrients for the blood to the brain. These transport system include those for various amino acids, glucose, and assorted nucleosides.²⁶ An approach to increasing the transcellular passage of drugs across the BBB into the brain is to design drugs that structurally resemble or can be linked to endogenous compounds that are transported into the brain by the carriers or transporters.^{27,28}

Different Transport System that operate from Blood to Brain at BBB	
Transport System	Typical Substrate
Metabolites	
Hexose	Glucose
Large neutral amino acid	Phenylalanine
Basic amino acid	Lysine
Acidic amino acid	Glutamate
Monocarboxylic acid	Lactate
Amine	Choline
Purine	Adenine
Nucleoside	Adenosine
Saturated fatty acid	Octanoate
Micronutrients	
Thiamine	Thramine
Pantothenic acid	Pantothenic acid
Biotin	Biotin
Vitamin B6	Pyridoxal
Riboflavin	Riboflavin
Niacinamide	Niacinamide
Carnitine	Carnitine
Lnositol	Myo-inositol
Other Peptides	
Transferin	Transferin
Enkephalins	Leu-enkephalin

Amino acid transporters

Several amino acids carrier systems are present in the BBB. These include a large neutral amino acid transporter, System L, a cationic amino acid transporter, System y⁺, the anionic amino acids transporter, System X⁻, and neutral and/or cationic amino acids transporter, System A and B⁰⁺.²⁹ System L has been most exploited for drug delivery purpose.³⁰ L-Dopa is transported by System L in the BBB and one of the drugs demonstrated to be taken up into the brain by a carrier mechanism.^{31,32} L-Dopa is an endogenous large amino acid and is precursor of the neurotransmitter dopamine. System L is also involved in the transport of the other drugs such as melphalan, baclofen and gabapentin.³³

Glucose transporters

The brain has a high metabolic demand for glucose. To accommodate the energy requirements of the CNS, glucose is transported from the blood to the brain through specific transport systems. The primary glucose

transporter (GLUT) present in the brain capillary in the capillary endothelial cells is GLUT1.³⁴ Compared to other nutrient transport /carrier systems in the BBB, GLUT1 has the highest capacity and therefore represents an attractive target for drug delivery to the CNS.

Monocarboxylic acid transporters

Systems for transporting monocarboxylic acids such as lactic acid, acetic acid both into and out of the CNS are abundant in the BBB. The best-characterized organic acid transporter in the BBB is the monocarboxylic acid transporter (MCT). The MCT has been detected on both the luminal (blood) and abluminal (brain) plasma membranes of the capillary endothelial cells.³⁵ An example of a drug entering the CNS through the MCT is salicylic acid.³⁶

Nucleoside transporters

There are two general types of nucleoside transporter facilitative nucleoside transporters that carry selective nucleosides either into or out of the cell, depending on the presence of a concentration gradient referred to as "equilibrative nucleoside transporters". And active, Sodium-dependent transporters that can move selective nucleosides into the cell against a concentration gradient referred to as "concentrative nucleoside transporters". The various equilibrative and concentrative nucleoside transporters display selectivity for either purine or pyrimidine nucleosides. Based on in vivo studies examining the BBB permeability of purine pyrimidine analogs, it would appear that the nucleoside transporters for purine based nucleoside are more active than the pyrimidine-selective transporter.³⁷

Vesicular transport in the BBB

There are two general types of vesicular transport processes fluid-phase endocytosis and adsorptive endocytosis. While both processes require energy and can be inhibited by metabolic inhibitors, only adsorptive endocytosis involves an initial binding or interaction of the molecule with the plasma membrane of the cell. However, several macromolecules of importance for normal brain function are transported from the blood into the brain through receptor-mediated endocytosis.

Transferrin receptor-mediated vesicular transport

Serum transferrin is a monomeric glycoprotein with a molecular weight of 80 kDa that is crucial for the transport of iron throughout the body.³⁸ Iron enters the cell as a complex with transferrin through an endocytic process that is initiated by the binding of transferrin to its receptor on the plasma membrane.³⁹ The brain capillary endothelial cells have a high density of transferrin receptors on their surface.⁴⁰ The binding of transferrin to its receptor on the brain capillary endothelial cells triggers the internalization of the transferrin-iron complex. Inside the brain endothelial cell, the iron is removed from the transferrin in the endosome, iron is released into the brain extracellular fluid, and transferrin and its receptor



are recycled back to the luminal (blood) plasma membrane.

Insulin receptor-mediated vesicular transport

Insulin is a pancreatic peptide hormone with important functions in glucose regulation. The presence of high-affinity insulin receptors on the luminal plasma membrane of brain microvessel endothelial cells and their involvement in the vesicular transport of insulin indicate that the peptide penetrates the BBB through a receptor-mediated transport process.^{41,42}

Different Transport Mechanisms for Drug/Peptides at BBB	
Transport mechanism	Peptide/drug
Receptor-mediated transcytosis	sAB1-40-Apolipoprotein J Apolipoprotein Arginine vasopressin sAB1-40 (Soluble amyloid) Insulin
Absorptive-mediated transcytosis	Cationized IgG Cationized BSA Cationized BSA-D-(ala2)-b-endorphin IgG(native, species homologus)
Carriers-mediated transport at the luminal side	Leucine enkephalin Delta sleep inducing peptide

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