



Review Article

Blood Brain Barrier and Various Strategies for Drug Delivery to Brain

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ABSTRACT

Many pharmaceuticals cannot access brain, though, has potential for treatment and this is mainly due to the potential blood brain barrier. To have a successful delivery, the challenges of anatomical and physiological aspects of those barriers need to be addressed. Though a considerable efforts were made in convincing those barriers, still designing a suitable delivery remains a major challenge. This review lists various strategies for the drug delivery to the brain. Sophisticated approaches like intracerebral delivery, intranasal delivery, barrier disruptions, receptor mediated transport, prodrugs, chemical drug delivery and many more were discussed. Limitations of some strategies were also discussed. Understanding the strategies along with the suitability of the therapeutic agent to undergo those strategic modifications would certainly promises the success of a brain drug delivery program. This a review made here would help the researcher in understanding the barrier and further modifying the therapeutic agent for the suitable drug or delivery.

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Introduction

The brain is a complex and a delicate organ and has inbuilt mechanism for protection. This protective mechanism also challenges therapeutics interventions and due to this many therapeutic agents are ineffective in many brain diseases. Understanding and manipulating the brain barrier are recent techniques for drug delivery to the brain. Many existing pharmaceuticals are rendered ineffective in the treatment of cerebral diseases due to our inability to effectively deliver and sustain them within the brain. General methods that can enhance drug delivery to the brain are therefore of great interest. Despite aggressive research, patients suffering from fatal or debilitating central nervous system diseases such as brain tumors, HIV encephalopathy, epilepsy, cerebrovascular diseases and neurodegenerative disorders, far outnumber those dying of all types of systemic cancer or heart diseases. The clinical failure of much potential effective therapeutics is often not due to a lack of drug potency, but rather to shortcomings in the method by which the drug is delivered¹.

The available strategies for CNS drug delivery may be broadly classified as either invasive (neurological based), pharmacologies-based, or physiologically based. The neurosurgical-based strategies include intraventricular drug infusion, intracerebral implants, and BBB disruption. The pharmacological-based strategies include the use of lipid carriers or liposomes. The physiologic based strategy takes advantage of the normal, endogenous pathways of either carrier-mediated transport of nutrients or receptor-mediated transport of peptides².

Blood brain barrier

The brain is probably one of the least accessible organs for the delivery of active pharmacological compounds. The same mechanisms that protect the brain from

foreign substances also restrict the entry of many potential therapeutic agents. Despite its relatively high blood flow, there are two physiological barriers separating the brain from its blood supply and they control the entry and exit of endogenous and exogenous compounds. One is the Blood-Brain Barrier (BBB) and the other is the Blood-Cerebrospinal Fluid Barrier (BCSFB). The BBB is the major barrier to the passage of active molecules from the blood compartment of the brain. The BBB, which segregates the brain interstitial fluid (ISF) from the circulating blood, is located at the level of the brain capillaries, where there is a convergence of different cell types: endothelial cells, pericytes, astrocytes and microglia (perivascular macrophages). The BCSFB separates the blood from the cerebro-spinal fluid (CSF) that runs in the subarachnoid space surrounding the brain. This barrier is located in the choroid plexus, and it is formed by epithelial cells held together at their apices by tight junctions, which limit paracellular flux. The CSF-facing surface of the epithelial cells, which secrete CSF into the ventricles, is increased by the presence of microvilli. The capillaries in the choroid plexus allow free movement of molecules via intracellular gaps and fenestrations^{3,4}. The brain is tightly segregated from the circulating blood by a unique membrane barrier, the blood-brain barrier (BBB)⁵⁻¹⁵. Capillaries in the brain and spinal cord lack the small pores that allow the rapid movement of solutes from circulation into the other organs. These capillaries are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions. These endothelial cells, together with perivascular elements such as astrocytes and pericytes, constitute the BBB⁵.

In brain capillaries, intercellular cleft, pinocytosis and fenestrae are virtually nonexistent: hence diffusion occurs

transcellularly. Therefore, only lipid soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB. In general, such exchange is overshadowed by other non specific exchanges. The brain is an organ of high metabolic rate and therefore of high blood flow. Cerebral blood flow takes up a considerable portion of the total cardiac output and the brains extensive network of capillaries could bring xenobiotics with easy reach of neurins^{5,16}. In addition to this, the BBB was degrading enzymes inside the endothelial cells that contain large densities of mitochondria. Enzymes and receptors found on the BBB include adenylate cyclase, guanylate cyclase, Na^+/K^+ adenosine triphosphate, alkaline phosphatase, catechol O- methyl transferase and DOPA decarboxylase^{5, 10,17-19}. These enzymes have the potential of degrading or blocking any therapeutic agents. Active efflux pumps have also been identified for CNS development²⁰. The existence of probenecid – sensitive, active pumps for organic ions has also been considered for drug delivery development for CNS²¹. Currently there are three classes of transporters for efflux of drugs from brain. They are monocarboxylic acid transporters, organic ion transporters and multi drug resistance transporter (P-glycoprotein)²⁰. The immunocytochemical detection of p-glycoprotein in brain microvessels^{2, 22,23} led to the hypothesis that p-glycoprotein is present in brain capillary endothelial membranes, specifically the endothelial luminal membrane²⁴. In this context, brain endothelial luminal membrane p-glycoprotein is presumed to act as an active efflux system preventing drug transport across the BBB. The brain/plasma drug ratios are volumes of distribution, which are a function of transport across astrocyte membranes and sequestration by cytoplasmic binding proteins, as well as

BBB permeability. P-glycoprotein may normally serve to retard the uptake into astrocytes of drugs that initially cross the BBB². The failure of systemically delivered drugs to effectively treat brain tumors and other CNS diseases is partly attributed to the inability of chemotherapeutic to cross the endothelial cell monolayer, which separates the blood from the brain and forms the blood-brain barrier (BBB)^{12,25-27}.

Brain tumor barrier

Brain tumors are neoplasms which vary in site of origin, morphology, growth potential, extent of invasiveness, tendency for progression and recurrence, and in response to treatment^{25,98,99}. There are significant obstacles to brain tumor drug delivery, which contribute to ineffective brain tumor therapy. Compared with the normal, ordered vasculature of healthy tissues, blood vessels in tumors are often highly abnormal; e.g., distended capillaries with leaky walls and sluggish flow, leading to inconsistent drug delivery. Furthermore, “leakage” from the tumor vasculature leads to an accumulation of interstitial fluid, subsequently increasing the intratumoral interstitial pressure, thus limiting the penetration of drugs into brain tumors^{25,100}. The failure of systemically delivered drugs to effectively treat brain tumors and other CNS diseases is partly attributed to the inability of chemotherapeutic to cross the endothelial cell monolayer, which separates the blood from the brain and forms the blood-brain barrier (BBB)^{12,25-27}. In brain tumors, permeability is a complex topic. There are at least two major variables involved. The first variable concerns the tumor microvessel populations, that is, BTB (Brain Tumor Barrier). The second major variable with regard to capillary permeability involves the spatial distribution of the target capillaries²⁸. The human body acts as an enormous sink in which the

majority of intravascularly administered drug will be distributed, not to the brain tumor, but to other body tissues. Once mixed with total body plasma, the drug distributes throughout the body tissues and is then eliminated²⁸. This would certainly lead to drug toxicity to the other tissues.

Strategies for drug delivery to brain

Intra ventricular drug infusion

Administration of drugs by injection or infusion into the lumbar subarachnoid space, the cerebral ventricles, or the basal cisterns of the brain have been important methods of treatment for patients with malignancies affecting the cerebro-spinal fluid (CSF) spaces or adjacent surfaces of the brain and spinal cord. The CSF-brain barrier, however, prevents significant drug penetration from the CSF spaces into the brain parenchyma^{25,29}. The CSF is in communication with the interstitial fluid of the brain, drug delivery to the brain can be attempted by delivering the drug to the cerebral ventricles. However, the slow diffusion is still a serious problem and hinders drug penetration. Intra ventricular injection can be a slow intravenous infusion and a larger molecule (neurotrophic factor will show only minimal brain penetration^{5,30}. After the infusion of drug into the ventricular compartment, there is a minimal distribution of the drug into the brain parenchyma from the ventricular or ependymal surface. Intraventricular infusion is an ideal way of delivering drugs to the surface of the brain, but is a poor mode of delivering drugs into the brain parenchyma. The ICV (Intra cerebro ventricular) injection of drug results in the distribution of the ependymal surface of only the ipsilateral brain because of the unidirectional flow of CSF within the brain. Intraventricular administration is like a slow, intravenous infusion and the drug is readily distributed

into the peripheral bloodstream after intraventricular drug infusion^{31,32}.

Intracerebral delivery

The most invasive approach to bypass the BBB is intracerebral delivery by direct injection, controlled release (Polymers^{5,33,34}, microspheres³⁵) by directing agents uniquely to an intracranial target. Interstitial drug delivery can theoretically yield high CNS drug concentrations with minimal systemic exposure and toxicity¹. Main complications are that one has to gain access through the skull. However the major and fundamental impediment is a very limited and slow diffusion within the brain away from the initial site of introduction⁵. Brain cells are tightly packed and make for limited interstitial space and unusually tortuous diffusion pathways. Diffusion may be very limited even for certain small-molecules⁵. The diffusion coefficient decreases with size^{5,36,37}. Many techniques have been developed for delivering drugs directly to the brain interstitium. One such methodology is the implantable pump which achieves continuous drug delivery. There are many commercial pumps available for sustained drug delivery to brain¹. Polymeric or lipid based devices can also deliver drug molecules at defined rates for specific periods of time^{1,38,39}. Drug delivery directly to the brain interstitium using polyanhydride wafers is also one of the methods. The fate of a drug delivered to the brain interstitium from the biodegradable polymer wafer can be predicted by a mathematical model based on (a) rates of drug transport via diffusion and fluid convection (b) rates of elimination from the brain via degradation, metabolism and permeation through capillary networks^{1,40}. Catheter systems have been in clinical use for several years. The ommaya reservoir^{25, 41}, for example, can deliver intermittent bolus injections of anticancer drugs directly to the brain tumor. Several

other infusion pumps can be implanted subcutaneously and they can be refilled by subcutaneous injection²⁵. The infusion pumps are capable of delivering drugs as a constant infusion over a prolonged period of time at a desired rate to the site of the intracranial tumor by the outlet catheter. These systems include the Infusaid pump (Infusaid, Norwood, MA, USA)^{25,42} the MiniMed PIMS system (MiniMed, Sylmar, CA, USA)^{25,43}, and the Medtronic SynchroMed system (Medtronic, Minneapolis, MN, SA)^{25,44}, which use compressed n favo pressure, a solenoid pump, and a peristaltic mechanism, respectively, to deliver the infused drug²⁵.

Intravascular drug delivery

Intravascular administration techniques include intraarterial therapy, which permits more selective drug delivery to brain tumors, high-dose chemotherapy, and intravenous applications that target drugs to the brain tumor without requiring surgical implantation of a foreign device. The advantage of administering a drug by the intra-arterial route is theoretically based upon the premise that a higher concentration of drug increases transition across the BBB. An intra-arterial infusion was clearly capable of delivering a greater amount of chloroethylnitrosourea into the brain tumor, up to fivefold, compared to the intravenous route. However, clinical trials of intra-arterial chemotherapy in the treatment of brain tumors have not yet demonstrated a clear improvement in survival rates over conventional intravenous administration²⁵. Targeting can improve the efficacy of anticancer therapy by distributing or providing more drug to cancer cells. Targeting can be achieved, for example, by liposomes, nanoparticles, and the use of external magnets to localize magnetized polymer microspheres and boron neutron capture therapy²⁵. They may be on intra

arterial therapy and intravenous therapy. The advantage of administering an anticancer drug by the intra-arterial route is theoretically based upon the premise that a higher concentration of drug increases transition across the BBB. The feasibility of permitting more selective drug delivery to brain tumors by catheterization of the carotid or vertebral arteries for intra-arterial administration of chemotherapeutic agents, such as the nitrosoureas, has been experimentally demonstrated^{25,45,46}. The success of the intra-arterial technique is limited by local complications related to arterial catheterization (as was mentioned above in the section “Catheter with pump systems”), and toxicity. A lack of treatment to the contralateral hemisphere and technical difficulty are further significant disadvantages of this technique²⁵.

Blood brain barrier disruption (BBBD)

The transient disruption of the BBB after the intracarotid arterial administration of mannitol was first observed 60 years ago^{25,47}. Currently, most therapeutic trials involving BBBD in patients with brain tumors have been conducted by intra-arterial infusion of a hypertonic solution of mannitol^{25,48,49}. Injection of an inert hypertonic solution results in its rapid diffusion of fluid across endothelial cell membranes, moving out of endothelial cells into the more hyperosmolar vascular lumen, and consequently osmotic disruption of the BBB as a result of endothelial cell shrinkage, and the subsequent opening of the tight junctions for a period of a few hours. The effect is related to molecular size, with the increased entry of smaller molecules. Earlier attempts to circumvent the BBB for therapeutic delivery was made by Kroll and neuwelt^{48,50} by using a transient osmotic opening approach⁵. Injection of hyperosmolar substances such as mannitol or arabinose causes BBB disruption

probably because the elevated concentration of these substances within brain capillaries extracts water from the endothelial cells and results in their shrinkage and opening of the corresponding intercellular gaps. Osmotic disruption also has been tested as a strategy for the delivery of macromolecular drugs such as monoclonal antibodies, nanoparticles and viruses^{1,48,51,52}. With some expertise, the resulting temporary BBB disruption can be exploited to increase drug delivery to the brain. However, because the procedure breaks down the self defence mechanism of the brain and leaves it vulnerable to damage or infection from all circulating chemicals or toxins, it is unacceptable and risky for most patients. Risk factors to be considered include the passage of plasma proteins, the altered glucose uptake, the expression of heat shock proteins, microembolism or abnormal neuronal function⁵. Thus osmotic opening can be one of the prominent strategies once if its demerits addressed.

Biochemical BBB opening

In contrast to osmotic disruption methods, biochemical opening utilizes the novel observation that normal brain capillaries appear to be unaffected when vasoactive leukotriene treatments are used to increase their permeability. Selective opening of brain tumor capillaries by intracarotid infusion of leukotriene C4 was achieved without concomitant alteration of the adjacent BBB^{5, 53}. However, brain tumour capillaries or injured brain capillaries appear to be sensitive to treatment with vasoactive leukotrienes and the permeation depends on molecular size. The mechanism was shown to be related to the abundance of g-glutamyl transpeptidase in normal brain capillaries resulting in a reduction of the enzymatic barrier in tumor endothelial cells^{1, 54}. Other agents such as bradykinin, histamine and the synthetic

bradykinin analog RMP-7 infusion selectively opens the blood brain tumour barrier¹. One of the most actively investigated compounds for its effects on brain edema and BBB permeability is arachidonic acid. Chan and fishman demonstrated that Amino Acid injected directly into the brain parenchyma would increase vascular permeability and result in vasogenic edema^{55, 56}. Kintos and co-workers demonstrated structural alterations of endothelial cells of pial arterioles after super fusion of the feline cortex with AA^{55,57}. Leukotriens are biologically active compound from the unsaturated fatty acid, arachidonic acid (AA) is the 5 – lipoxygenase pathway⁵⁵ which can be used for BBB opening. Other biochemical opening agents are bradykinin, histamine, serotonin, which is promising agents for BBB delivery.

Small molecules

Blood-brain barrier drug targeting strategies may not be needed if high throughput screening programs lead to “small molecules” that crosses the BBB unassisted. However, this line of reasoning is problematical for two reasons. First, it is difficult to generate small molecule peptidomimetic drugs that retain a high affinity binding and specificity for the target receptor². Secondly, a molecule is not small unless it has a molecular weight less than a 400 to 600 dalton threshold^{2,31}. Even then, a drug with a molecular weight under 500 d may not cross the BBB in pharmacologically active amounts unless the drug is lipid soluble. These dual criteria (lipid solubility, molecular weight less that 500 d) are unlikely to be fulfilled by small molecule mimetic drugs².

Inhibition of P-glycoprotein efflux

P-glycoprotein represents an ATP-dependent efflux pathway that confers

resistance to brain cells by allowing them to move a variety of chemotherapeutic drugs out of the cell against a concentration gradient⁵⁸⁻⁶⁰. This efflux prevents most of the drugs that accessed the brain by removing from the brain cells. P-glycoprotein appears to be localized primarily to the luminal capillary membrane of the brain, and the number of drugs that are transported by this system may be quite large^{58,59}. Immunohistochemically, P-glycoprotein has been demonstrated in malignant glioma tumor cells^{58,61,62}. Inhibiting P-glycoprotein would increase both extracellular and intracellular drug concentration without increasing the amount of drug administered. This is an avenue of modifying brain tumour therapy that must be explored⁵⁸.

Lipophilic analogs

Overton^{5,63,64} and Meyer^{5,65,66} discovered first that opioid potency in a set of congeners tends to increase as the oil/water partition coefficient increases and this interested the research in defining the lipophilicity and its role in CNS activity⁵. Lipophilic drug analogs are used to overcome limitations of the parent drug, such as poor cerebrovascular permeability. Carmustine is an alkylating agent used to treat brain tumors, multiple myeloma, Hodgkin's disease and non Hodgkin's lymphomas. More than 20 lipophilic carmustine analogs were studied in clinical trials which demonstrated that the antineoplastic activity of these analogs was, however, inversely proportional to their lipophilicity^{25,67,68}. Most of these lipophilic analogs demonstrated decreased alkylating activity and increased dose-limiting toxicity when compared to carmustine, perhaps by affecting drug-receptor interactions²⁵. Increasing lipophilicity with the intent to improve membrane permeability might not only make chemical handling difficult, but might also increase the rate of oxidative metabolism by cytochrome P450 and other

enzymes^{5,69,70}. Hence, to improve bioavailability, the effects of lipophilicity on membrane permeability and first pass metabolism have to be advanced^{5,69,71}.

Carrier mediated transport

The delivery of drugs to the brain via BBB carrier mediated transport is most likely to occur when the drug is modified to take on the structure of an endogenous nutrient². The carrier-mediated drug delivery approach takes advantage of facilitating endogenous transport systems that are present in brain endothelial cells. A number of carrier transport systems at the BBB are responsible for brain uptake of nutrients (and their analogs) from the systemic circulation²⁵. Thus, transport systems exist for glucose^{25,72}, amino acids^{25,73,15,74}, choline⁷⁵, vitamins^{76,77}, low density lipoprotein (LDL)^{14,97}, and nucleosides⁷⁷. The formation of a nutrient/drug conjugate would most likely induce structural changes within the nutrient beyond that tolerated by the stereospecific pore within the transporter protein. It is conceivable that some drug/nutrient conjugates could undergo carrier-mediated transport through the BBB, but the most likely event is carrier-mediated transport of a drug that has been modified such that the drug itself has a structure analogous to an endogenous nutrient². For example, L-DOPA has the structure of a neutral amino acid. Drugs that undergo carrier-mediated transport through the BBB other than L-DOPA include α -methyl-DOPA, melphalan, α -methyl-para-tyrosine, and gabapentin, which all undergo transport via the BBB neutral amino acid transport system². An example of converting the structure of a non-transportable drug into a pseudo-nutrient structure would be the case of a monoamine that normally does not undergo significant transport through the BBB. Rather than attaching this drug to an amino acid, an alternative approach would be to convert the monoamine into an α -amino acid. This

pro-drug would undergo transport through the BBB via the neutral amino acid carrier. Once in the brain, the pro-drug would be decarboxylated back to the parent monoamine via aromatic amino acid decarboxylase^{2,78}.

Intranasal Delivery

Drug delivered intranasally are transported along olfactory sensory neurons to yield significant concentrations in the cerebro spinal fluid (CSF) and olfactory bulb. Although absorption across the respiratory epithelium is the major transport pathway for nasally-administered drugs and may represent a potentially time saving route for the administration of certain systemic drugs delivered in chronic medication protocols (e.g., epinephrine or vasopressin), problem of BBB-mediated exclusion of brain-therapeutic agents to be of greater immediate concern³. The olfactory pathways may be broadly classified into two possible routes: the olfactory nerve pathway (axonal transport) and the olfactory epithelial pathway. Axonal transport is considered as a slow route whereby an agent enters the olfactory neuron via endocytotic or pinocytotic mechanisms and travels to the olfactory bulb by utilizing the same anterograde axonal transport mechanisms the cell uses to transport endogenous substances to the brain. Depending on the substance administered, axonal transport rates range from 20-400 mm/day to a slower 0.1-4 mm/day³. The epithelial pathway is a significantly faster route for direct nose-to-brain transfer, whereby 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. Then the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and subsequently into the systemic circulation³.

Receptor mediated Transport

This is a very broad area because any receptor-mediated transport system in the BBB can be elected as a target. The considerations about drug delivery in a facilitated transport system are different from those involving simple diffusion. First, a facilitated transport system can be characterized by the Michaelis-Menten constants, K_m (the concentration at which the reaction velocity is half maximal), and V_{max} (the limiting velocity as the concentration approaches infinity). An important factor in the facilitated transport of drugs is the plasma concentration of the native substrate for the receptor²⁸. Receptor mediated drug delivery to the brain employs chimeric peptide technology, wherein a non-transportable drug is conjugated to a BBB transport vector. The latter is a modified protein or receptor specific monoclonal antibody that undergoes receptor-mediated transcytosis through the BBB *in vivo*. Conjugation of drug to transport vector is facilitated with the chemical linkers, avidin – biotin technology, polyethylene glycol linkers or liposomes. Multiple classes of therapeutics have been delivered to the brain by the chimeric peptide technology, including peptide based pharmaceutical such as a vasoactive peptide analog or neurotrophins such as brain derived neurotropic factor, antisense therapeutics including peptide nucleic acids^{1,79,80}. Adsorptive mediated transcytosis, a mechanism of brain uptake that is related to receptor mediated transcytosis, operates for peptides and proteins with a basic isoelectric point (cationic proteins) and for some lectins (glycoprotein binding proteins). The initial binding to the luminal plasma membrane is mediated by electrostatic interactions with anionic sites or by specific interactions with sugar residues respectively^{1,81}. Nanoparticle have also been used as a transport vectors for peptides. Nanoparticle consist of colloidal polymer particles of poly – butyl cyanoacrylate with the desired peptide absorbed onto the surface and then coated

with polysorbate 80. Nanoparticles have been used as a vector for the delivery of hexapeptide dalargin. Intravenous injection of the vector dalargin produces analgesia, while dalargin alone does not^{1, 82}. The most probable transport pathway seems to be endocytosis by the blood capillary endothelial cells following adsorption of blood plasma components, most likely apolipoprotein E after intravenous injection. These particles interact with the low density lipoprotein receptor on the endothelial cells and then gets internalized. After internalization by the brain capillary endothelial cells, the drug release in these cells by desorption or degradation of the nanoparticles and diffuses into the residual brain. Alternatively, transport may also occur by transytosis of the nano particles with drug across the endothelial cells¹.

Prodrugs

An alternative strategy for lipophilic drug analogs is the design of lipophilic prodrugs. Whereas drug analogs are active themselves, pharmacologically inactive prodrugs require a chemical or biochemical transformation to achieve the active form within the body^{25,84,85}. Prodrugs are designed to overcome pharmaceutical and (or) pharmacokinetic limitations of the parent molecule which would otherwise be of limited clinical use, such as poor BBB penetration. To enhance a drug's penetration into the brain by passive diffusion, the simplest approach is to use a lipophilic prodrug strategy²⁵. Many potent small anticancer drugs are lipophilic enough to cross the BBB and, therefore, a lipophilic prodrug approach may not necessarily be the most appropriate way to accomplish better brain tumour drug delivery. However, lipophilic ester prodrugs of the anticancer agent chlorambucil have been developed to increase efficacy in the treatment of brain tumours^{25,86,87}. Increased lipophilicity over the parent drug alone does not ensure

improved drug efficacy. While enhanced lipophilicity may improve permeation across the BBB, it also tends to increase uptake into other tissues, causing an increased tissue burden. Moreover, both bioconversion selectivity (serum vs. brain) and rate of bioconversion in the target tissue (i.e., brain tumor) should also be taken into account when designing bioreversible prodrugs²⁵.

Pegylated immunoliposomes

The carrying capacity of the vector could be greatly expanded by attaching liposomes to the vector, because up to 1 0,000 small molecules can be sequestered within a single liposome. Liposomes do not normally transport across the BBB because these devices are too large to undergo lipid-mediated transport across the endothelial membrane^{2,88}. Liposomes are rapidly removed from the bloodstream via uptake by cells lining the reticulo-endothelial system^{2,89}. Because of this rapid removal, the plasma AUC of liposomes is markedly reduced, and this results in unfavorable pharmacokinetics. The rapid removal of liposomes from plasma may be inhibited by attachment of polyethylene glycol polymers to the surface of the liposomes^{2,90}. The dual objectives of optimizing both BBB permeability, via vector-mediated drug delivery across the BBB, and optimizing plasma pharmacokinetics, via the use of pegylation technology, may be achieved by tethering the receptor-specific Mab to the tip of the polyethylene glycol tail^{2,91}. The construction of such a complex is made possible by preparation of a bifunctional polyethylene-glycol derivative containing a phospholipid at one end and a maleimide group at the other end, which allows for the formation of a stable thioether linkage after conjugation².

Future need for brain target drug delivery

Need to target therapeutics to specific brain regions or cell types

Since drugs that enter the brain via the transvascular system deliver to all parts of the brain, the development of a region specific targeting system may be difficult for protein drugs. In the case of non-viral gene transfer, regional therapy is possible, owing to the region-specific expression of certain genes in the brain^{92,93}. The use of the promoters of these region-specific genes in the engineering of expression plasmids encoding therapeutic genes can enable the selective expression of a transgene to a specific region of the brain. Certain diseases are localized to specific cells in brain, e.g., brain cancer and glial cells, multiple sclerosis and oligodendrocytes. Once a drug is targeted across the BBB, it may be advantageous to target the drug to a specific cell. This may be possible with the use of bispecific antibodies, which are engineered to recognize dual targets: the BBB and the specific cell type in brain⁹².

Need to understand the toxicity associated with brain drug delivery

Nanomaterials or cellular delivery systems may affect brain capillary endothelial function, including transcytosis and BBB disruption. Thus, it is important to initiate the long term administration of new brain drug targeting systems early in the preclinical research, and to investigate for any untoward cellular effects of these systems⁹². While most toxicity will be detected in the pharmacology and toxicology required by the studies or in the phase I clinical trial in small numbers of patients, it is crucial that potential toxic manifestations of the targeting system to be evaluated early in the preclinical research⁹².

Need to improve understanding of BBB transport systems

There is a lack of molecular information describing the interaction of members of the solute carrier gene family and ATP-binding cassette (ABC) gene family of transporters that participate in the active efflux transport of drugs and metabolites from brain to blood. The challenge in BBB efflux is to identify the *pairs* of transporters that participate in the active efflux of a given drug. In particular, there is a need for expanding the knowledge on how BBB efflux systems are modulated in physiological and pathological conditions⁹².

Need for *in vivo* evaluation of brain drug pharmacokinetics

Most therapeutic trials involving drug delivery to the CNS lack basic pharmacology regarding agent delivery^{92,94}. Measurement of brain delivery pharmacokinetics should be a regular component of preclinical, and some clinical studies. Ideally, any new brain drug targeting system should enable the investigator to demonstrate *in vivo* CNS pharmacological effects following IV administration at reasonable doses of the drug. Methods for quantitative measurements of brain drug uptake remain an issue. Many studies of BBB permeability use the log BB, where BB is the ratio of brain drug concentration to the blood drug concentration at some terminal time point, e.g. 60 min, after administration^{92,95}. The log BB is largely a measure of brain drug volume of distribution, which is determined by the cytoplasmic binding of drug to a much greater degree than BBB permeability^{92,96}. A better measure is the percent of injected dose/gram brain.

Need to identify new brain drug targeting systems

Multiple combinatorial display systems, incorporating either yeast or phage technology, are presently being mined within the pharmaceutical industry for new drug discovery targets. These combined systems

could also be used to screen for new brain drug targeting systems⁹². Other target systems such as receptor mediated or lipid based drug deliver would also be a good candidate for the drug development program. Drug or drug delivery targeting Pglycoprotein efflux would be much beneficial for those drugs already gained access to the brain.

Need to speed development and application of molecular imaging probes and targeted contrast agents

Imaging techniques have the potential to significantly accelerate brain drug development. Targeted molecular probes for MRI and nuclear medicine will improve the specificity of imaging data and aid drug discovery efforts. Imaging agents typically have a much smaller market capitalization than therapeutics, so often are not pursued by the pharmaceutical industry. Many compounds that have the unfavorable therapeutic potential could be excellent candidates for imaging probes. Improved access to pharmaceutical databases could facilitate development of molecular imaging probes⁹².

Conclusions

The challenges of designing a drug delivery though faces a great challenge, a thorough understanding of the anatomical and physiological barrier would help the therapeutic agents in convincing those barriers. Many interdisciplinary fields of science, such as chemistry, novel drug deliveries, in silico techniques and many more need to participate in drug or drug delivery program for success of suitable therapeutic agents. Screening methods for *in vitro* studies to evaluate the efficiency of the proposed drugs/drug delivery should be widely available and should be easily correlated to the real target tissues. Addressing the above concerns would help the drug design more efficient.

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Table 1. Unique features of brain tumour barrier and blood brain barrier²⁵

Blood brain barrier	Brain tumour barrier
Tight (High-resistance) intracellular junctions	Heterogeneous distribution of microvasculature
Absence of fenestration	Elevation of interstitial pressure inside the tumour
Deficiency in pinocytic vesicular traffic	Disrupted tight junctions
Abundant mitochondria (high metabolic capacity)	Hypoxia
Active drug efflux transporters	Over – expression of bioreductive enzymes and drug resistance mechanisms

Table 2. Small molecules having access to blood brain barrier²

Drug type	Blood – brain barrier transport
Peptides	No
Recombinant Proteins	No
Monoclonal Antibodies	No
Antisense oligonucleotides	No
Lipid soluble small molecules (Molecular weight less than 500 Daltons)	Yes
Lipid soluble small molecules (Molecular weight More than 500 Daltons)	Minimal

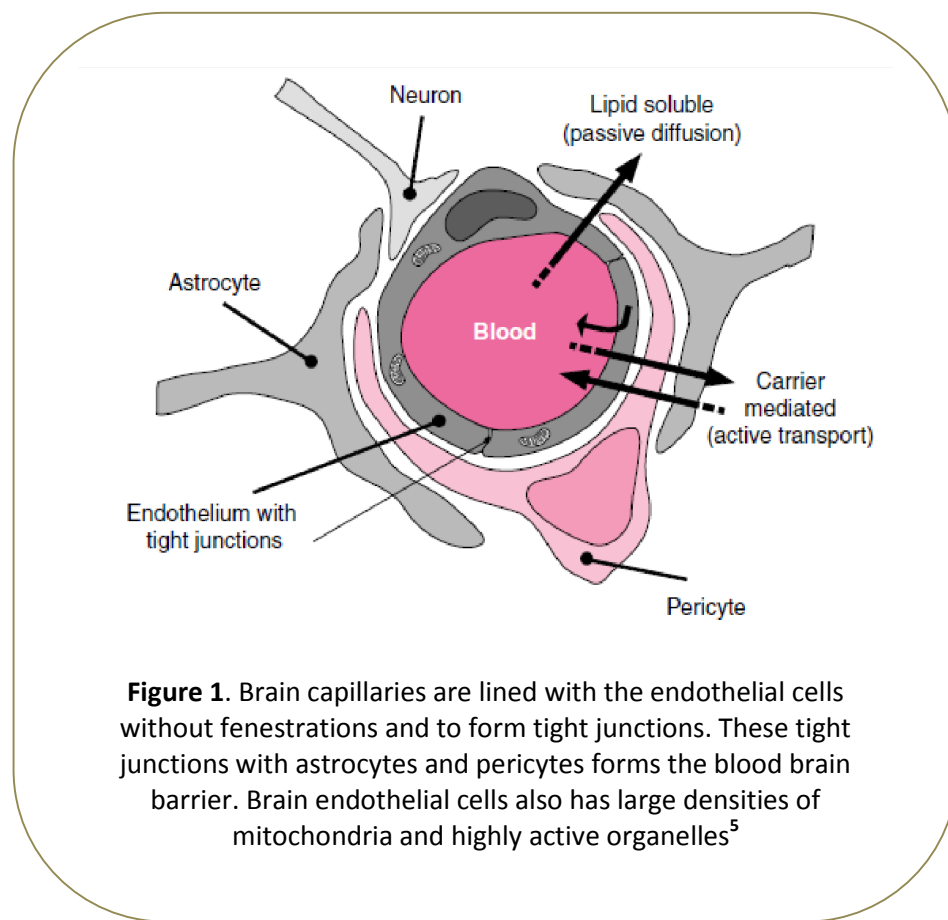


Figure 1. Brain capillaries are lined with the endothelial cells without fenestrations and to form tight junctions. These tight junctions with astrocytes and pericytes forms the blood brain barrier. Brain endothelial cells also has large densities of mitochondria and highly active organelles⁵

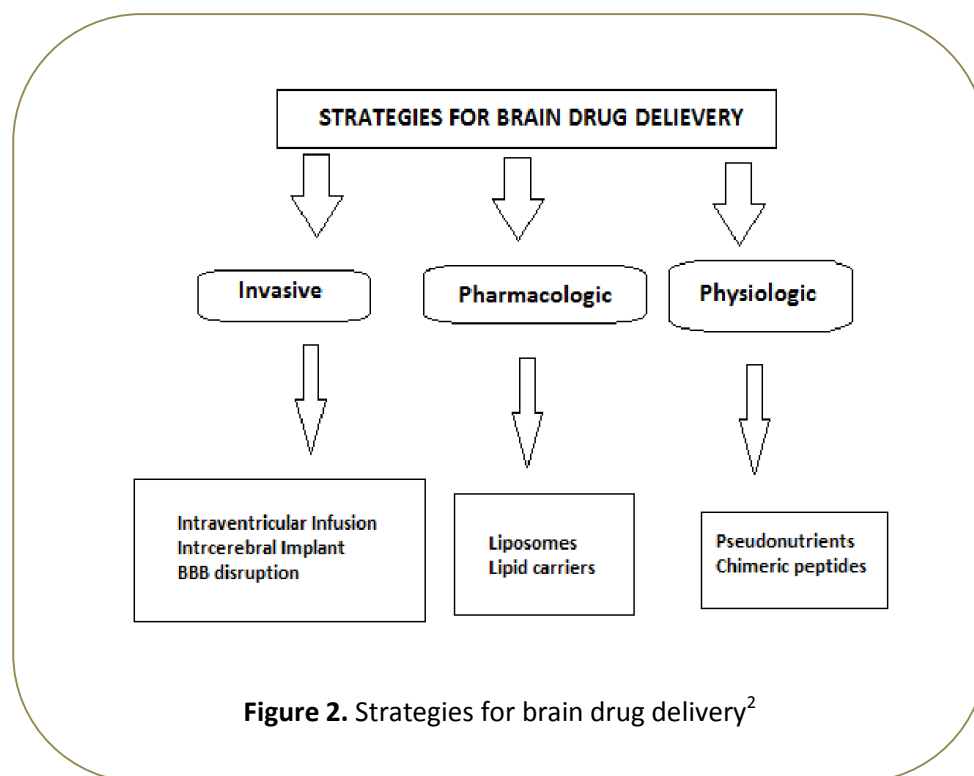


Figure 2. Strategies for brain drug delivery²