Poles apart Inimitability of Brain Targeted Drug Delivery system in Middle of NDDS

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Abstract:
In spite of an impressive increase in CNS drug discovery, the biggest obstacle remains the effective delivery of these agents across the blood brain barrier, hence the delivery of therapeutic agents to the brain is limited by the presence of the Blood-Brain Barrier (BBB). In the basic science of brain physiology and disease in the past decade, delivery issues have received minimal attention. Current estimates are that 98% of all small molecule drugs minimally cross the BBB, and negligible amounts of large molecule drugs cross the BBB, except leakage in areas of BBB dysfunction.
Lipid soluble drugs with a molecular weight under 400-600 daltons are transported to through a blood-brain barrier by lipid mediated transport. This hindrance has slowed the application of pharmacotherapy and immunotherapy in brain diseases. Hence it is important to unite brain targeted drug discovery and CNS drug delivery as early as possible for CNS drug development process. In this report we review the major advances in brain drug targeting research, including approaches to circumvent the BBB for brain delivery by making use of endogenous transport mechanisms or bypassing the BBB altogether. Among all the approaches used for increasing brain delivery of drugs, the most accepted method is the use of the physiological approach. The physiological approach use specific receptors already expressed on the capillary endothelial cells forming the BBB and necessary for the survival of brain cells. This review intends to detail the recent advances in the field of brain-targeting and drug delivery to CNS.

Keywords: Antioxidant activity, PRAC, *Oxalis corniculata*

Review Paper

INTRODUCTION

The brain is a delicate organ, and evolution built very efficient ways to protect it. The same mechanisms that protect it against intrusive chemicals can also frustrate therapeutic interventions. 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 can enhance drug delivery to the brain. Despite aggressive research, patients suffering from fatal central nervous system diseases, such as brain tumors, HIV encephalopathy, epilepsy, cerebrovascular diseases and neurodegenerative disorders, far outnumbered. The clinical failure of much potentially effective therapeutics is often not due to a lack of drug potency but rather to shortcomings in the method by which the drug is delivered. In response to the insufficiency in conventional delivery mechanisms, aggressive research efforts have recently focused on the development of new strategies to more effectively deliver drug molecules to the CNS.

Various routes of administration as well as conjugations of drugs, e.g. with liposomes and nanoparticles are considered. Some routes of direct administration to the brain are non-invasive such as transnasal route whereas others involve entry into the CNS by devices and needles such as in case of intrathecal and intracerebroventricular is considered along with sustained and controlled release delivery.

Systemic therapy by oral and parenteral routes to optimize the CNS action of drugs. Among the three main approaches to drug delivery to the CNS - systemic administration, injection into CSF pathways, and direct injection into the brain, the greatest developments is anticipated to occur in the area of targeted delivery by systemic administration. Cell and gene therapies will play an important role in the treatment of neurological disorders in the future. Besides development of new products, these include application of innovative methods of delivery to older drugs to improve their action and extend their patent life[2]. Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. The brain (central nervous system) is protected by barriers which control the entry of compounds into the brain, thereby regulating brain homeostasis. Brain is tightly segregated from the circulating blood by a unique membranous barrier - the Blood Brain Barrier (BBB)[1,9]. The majority of drugs that are used to treat CNS disease have a molecular weight between 150 and 500 Da and a log octanol/water partition coefficient between -0.5 and 6.0[5].

It is generally assumed that charged molecules cannot readily penetrate the BBB; thus, for a drug that is partially ionized at physiological pH 7.4, it is the uncharged fraction that determines the diffusion gradient across the BBB and forms the driving force for any passive diffusive movement of drug[10].

BARRIERS TO CNS DRUG DELIVERY

The failure of systemically delivered drugs to effectively treat many CNS diseases can be rationalized by considering a number of barriers that inhibit drug delivery to the CNS[4].

- **blood-brain barrier**
- **blood-cerebrospinal fluid barrier**
- **blood-tumor barrier**

Blood-Brain Barrier

It is now well established that the BBB is a unique membranous barrier that tightly segregates the brain from the circulating blood. The CNS consist of blood capillaries which are structurally different from the blood capillaries in other tissues; these structural differences result in a permeability barrier between the blood within brain capillaries and the extracellular fluid in brain tissue. Capillaries of the vertebrate brain and spinal cord lack the small pores that allow rapid movement of solutes from circulation into other organs; these capillaries are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions. Tight epithelium, similar in nature to this barrier, is also found in other organs (skin, bladder, colon, and lung) .This permeability barrier, comprising, the brain capillary endothelium, is known as the BBB.

Ependymal cells lining the cerebral ventricles and glial cells are of three types;

➢ **Astrocytes** form the structural frame work for the neurons and control their biochemical environment. Astrocytes foot processes or limbs that spread out and abutting one other, encapsulate the capillaries are closely associated with the blood vessels to form the BBB.

➢ **Oligodendrocytes** are responsible for the formation and maintenance of the myelin sheath, which surrounds axons and is essential for the fast transmission of action potentials by salutatory conduction. Microglias are blood derived mononuclear macrophages. The tight junctions between endothelial cells results in a very high trans-endothelial electrical resistance of 1500-2000.cm2 compared to 3-33.cm2 of other tissues

which reduces the aqueous based para-cellular diffusion that is observed in other organs.

➢ **Micro-vessels** make up an estimated 95% of the total surface area of the BBB, and represent the principal route by which chemicals enter the brain. Vessels in brain were found to have somewhat smaller diameter and thinner wall than vessels in other organs.

Also, the mitochondrial density in brain micro-vessels was found to be higher than in other capillaries not because of more numerous or larger mitochondria, but because of the small dimensions of the brain micro-vessels and consequently, smaller cytoplasmic area. In brain capillaries, intercellular cleft, pinocytosis, and fenestrae are virtually nonexistent; exchange must pass trans-cellularly. Therefore, only lipid-soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB. In capillaries of other parts of the body, such exchange is overshadowed by other nonspecific exchanges. Despite the estimated total length of 650km and total surface area of 12 m^2 of capillaries inhuman brain, this barrier is very efficient and makes the brain practically inaccessible for lipid- insoluble compounds such as polar molecules and small ions. As a consequence, the therapeutic value of many promising drugs is diminished, and cerebral diseases have proved to be most refractory to therapeutic interventions. Given the prevalence of brain diseases alone, this is a considerabl problem. Practically all drugs currently used for disorders of the brain are lipid-soluble and can readily cross the BBB following oral administration. Although antimicrobial blactam antibiotics, when administered intracerebro ventricularly, cause severe convulsion, fortunately these antibiotics, when administered intravenously or orally, do not cause such central nervous system (CNS) side effect because their limited transport across the blood–brain barrier (BBB). Further, in spite of being well distributed into various tissues, a lipophilic new quinolone antimicrobial agent, grepafloxacin, cannot enter the brain, res ulting in the avoidance of CNS side effects such as headache and dizziness due to the displacement of g-aminobutyric acid (GABA) from the GABA receptor binding sites. On the other hand, benzodiazepines such as diazepam have been used as sedative-hypnotic agents, because these lipophilic drugs readily cross the BBB. However, the BBB transport of an immunosuppressive agent, cyclosporin A, which is more lipophilic than diazepam, is highly restricted. Similarly, almost all of the lipophilic anticancer agents such as doxorubicin, epipodophylotoxin and Vinca alkaloids (e.g., vincristine and vinblastine) hardly enter the brain, causing difficulty in the treatment of brain tumors. Although levodopa, which is useful for treatment of Parkinson's disease, is very hydrophilic, it can readily penetrate the BBB.

What mechanisms underlie these diverse BBB transport characteristics of drugs which are apparently structurally and pharmacologically unrelated? In order to avoid overlap with this section, the drug transport across the BBB of small-molecular drugs by carrier-mediated transport and of peptide drugs by the adsorptive-mediated transcytosis.

Some regions of the CNS do not express the classical BBB capillary endothelial cells, but have micro-vessels similar to those of the periphery. These areas are adjacent to the ventricles of the brain and are termed the circumventricular organs (CVOs). The CVOs include the choroid plexus, the median eminence, neurohypophysis, pineal gland, organum vasculosum of the lamina

terminalis, subfornical organ, subcommisaral organ and the area postrema.

Though in the CVO brain regions the capillaries are more permeable to solutes, the epithelial cells of the choroid plexus and the tanycytes of other regions form tight junctions to prevent transport from the abluminal extracellular fluid (ECF) to the brain ECF. The choroid plexus may be of importance when considering the transport of peptide drugs, because it is the major site of cerebrospinal-fluid (CSF) production, and both the CSF and brain ECF freely exchange.

The BBB also has an additional enzymatic aspect. Solutes crossing the cell membrane are subsequently exposed to degrading enzymes present in large numbers inside the endothelial cells that contain large densities of mitochondria, metabolically highly active organelles. BBB enzymes also recognize and rapidly degrade most peptides, including naturally occurring neuropeptides.

Finally, the BBB is further reinforced by a high concentration of P-glycoprotein (Pgp), active – drug-efflux-transporter protein in the luminal membranes of the cerebral capillary endothelium. This efflux transporter actively removes a broad range of drug molecules from the endothelial cell cytoplasm before they cross into the brain parenchyma[4].
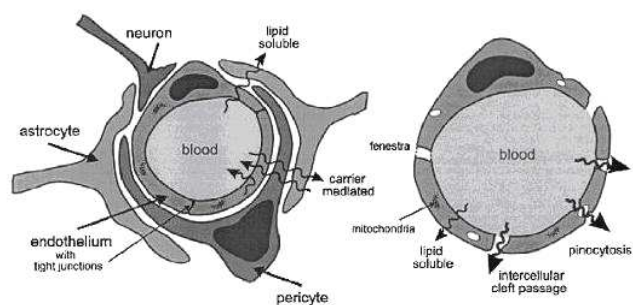

Fig. 1: Schematic representation of all these BBB properties using a comparison between brain and general capillaries

Blood-Cerebrospinal Fluid Barrier

The second barrier that a systemically administered drug encounters before entering the CNS is known as the blood-cerebrospinal fluid barrier (BCB). Since the CSF can exchange molecules with the interstitial fluid of the brain parenchyma, the passage of blood-borne molecules into the CSF is also carefully regulated by the BCB. Physiologically, the BCB is found in the epithelium of the choroids plexus, which are arranged in a manner that limits the passage of molecules and cells into the CSF. The choroid plexus and the arachnoid membrane act together at the barriers between the blood and CSF. On the external surface of the brain the ependymal cells fold over onto themselves to form a double layered structure, which lies between the dura and pia, this is called the arachnoid membrane. Within the double layer is the subarachnoid space, which participates in CSF drainage. Passage of substances from the blood through the arachnoid membrane is prevented by tight junctions.. The arachnoid membrane is generally impermeable to hydrophilic substances, and its role is forming the Blood-CSF barrier is largely passive. The choroid plexus forms the CSF and actively regulates the concentration of molecules in the CSF. The choroid plexus consist of highly vascularized, "cauliflowerlike" masses of pia mater tissue that dip into pockets formed by ependymal cells. The preponderance of choroid plexus is distributed throughout the fourth ventricle near the base of the brain and in the lateral ventricles inside the right and left cerebral hemispheres. The cells of the choroidal epithelium are modified and have epithelial characteristics. These ependymal cells have microvilli on the CSF side, basolateral interdigitations, and abundant mitochondria. The

ependymal cells, which line the ventricles, form a continuous sheet around the choroid plexus. While the capillaries of the choroid plexus are fenestrated, non-continuous and have gaps between the capillary endothelial cells allowing the free-movement of small molecules, the adjacent choroidal epithelial cells form tight junctions preventing most macromolecules from effectively passing into the CSF from the blood. However, these epithelial- like cells have shown a low resistance as compared the cerebral endothelial cells, approximately 200 Ω.cm2, between blood and CSF[4].

In addition, the BCB is fortified by an active organic acid transporter system in the choroids plexus capable of driving CSF-borne organic acids into the blood. As a result a variety of therapeutic organic acids such as the antibiotic penicillin, the anti-neoplastic agent methotrexate, and the antiviral agent zidovudine are actively removed from the CSF and therefore inhibited from diffusing into the brain parenchyma. Furthermore, substantial inconsistencies often exist between the composition of the CSF and interstitial fluid of the brain parenchyma, suggesting the presence of what is sometimes called the CSF-brain barrier[11]. This barrier is attributed to the insurmountable diffusion distances. The insurmountable diffusion distances required for equilibration between the CSF and the brain interstitial fluid. Therefore, entry into the CSF does not guarantee a drug's penetration into the brain[4].

Blood-Tumor Barrier

Intracranial drug delivery is even more challenging when the target is a CNS tumor. The presence of the BBB in the microvasculature of CNS tumors has clinical consequences. For example, even when primary and secondary systemic tumors respond to chemotherapeutic agents delivered via the cardiovascular system, intracranial metastases often continue to grow. In CNS malignancies where the BBB is significantly compromised, a variety of physiological barriers common to all solid tumors inhibit drug delivery via the cardiovascular system. Drug delivery to neoplastic cells in a solid tumor is compromised by a heterogeneous distribution of microvasculature throughout the tumor interstitial, which leads to spatially inconsistent drug delivery. Furthermore, as a tumor grows large, the vascular surface area decreases, leading to a reduction in trans-vascular exchange of blood-borne molecules[4]. At the same time, intra-capillary distance increases, leading to a greater diffusional requirement for drug delivery to neoplastic cells and due to high to high interstitial tumor pressure and the associated peri-tumoral edema leads to increase in hydrostatic pressure in the normal brain parenchyma adjacent to the tumor. As a result, the cerebral microvasculature in these tumor adjacent regions of normal brain may be even less permeable to drugs than normal brain endothelium, leading to exceptionally low extra-tumoral interstitial drug concentrations[12]. Brain tumors may also disrupt BBB, but these are also local and non-homogeneous disruptions[13].

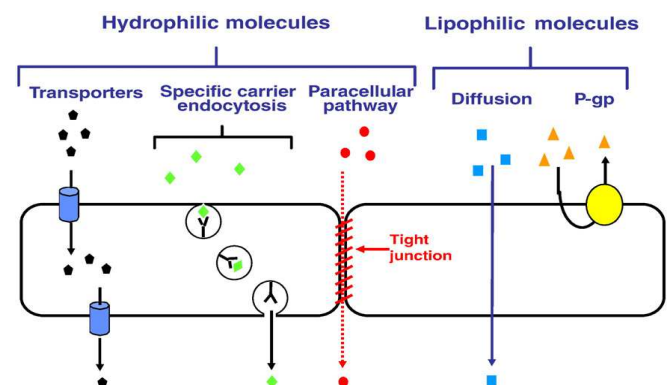### DRUG DELIVERY SYSTEMS TARGETING BRAIN

Fig. 2: Schematic representation of the transport of molecules across the BBB

- Small hydrophilic molecules such as amino acids, glucose, and other molecules necessary for the survival of brain cells use transporters expressed at the luminal (blood) and basolateral (brain) side of the endothelial cells.

- Larger and/or hydrophilic essential molecules such as hormones, transferrin for iron, insulin, and lipoproteins use specific receptors that are highly expressed on the luminal side of the endothelial cells. These receptors function in the endocytosis and transcytosis of compounds across the BBB.

- Small lipophilic molecules can diffuse passively across the BBB into the brain but will be exposed to efflux pumps (P-glycoprotein (P-gp), some Multidrug Resistance Proteins (MRP), Breast cancer Resistance Protein (BCRP) and others) expressed on the luminal side of the BBB and exposed to degrading enzymes (ecto- and endo-enzymes) localized in the cytoplasm of endothelial cells before brain penetration. To bypass the BBB and to deliver therapeutics into the brain, three different approaches are currently used — invasive, pharmacological and physiological.

These are considered below:

APPROACHES TO BYPASS BBB
A) Invasive approach

These are physical based techniques include the use of:

1) Intracerebro-ventricular infusion,

2) Convection-enhanced delivery

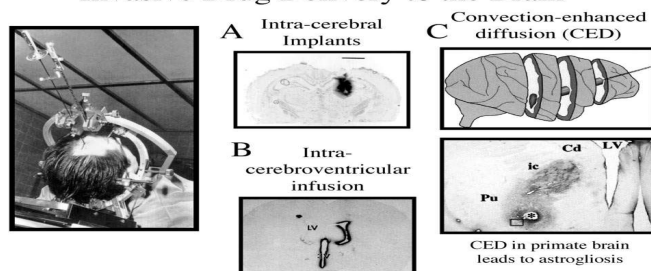3) Polymer or microchip systems

4) Disruption of BBB.

Fig. 3: It shows trans-cranial drug delivery to the brain

A: Autoradiogram of rat brain 48 h after an intracerebral implantation of a polymer carrying radiolabeled NGF.15 The size of the polymer approximates the magnification bar, indicating the NGF has not significantly diffused from the implantation site. B: Autoradiogram of rat brain 24 h after an intracerebroventricular injection of BDNF into an LV.16 The BDNF distributes to the ependymal surface of the ipsilateral LV and the third ventricle (3V), but not into brain parenchyma. C: Convection enhanced diffusion in the primate brain forces fluid through the brain tissue. The direction of fluid flow, principally via white matter tracts,19 can be traced with immunocytochemistry using an antibody to GFAP, which shows an astrogliotic reaction in the path of fluid flow.20 The hole in the brain left by the catheter is noted by the asterisk. The fluid moved from the catheter in the putamen (Pu) via the internal capsule (ic) white matter to the caudate (Cd)[6].

1. Intra-cerebro-ventricular (ICV) infusion

It has been reported that the concentration of a drug in the brain is only 1–2% of the CSF concentration at just 1–2 mm from the surface. The drug eventually distributes to the general circulation, where the drug then enters the brain parenchyma following transport across the BBB.
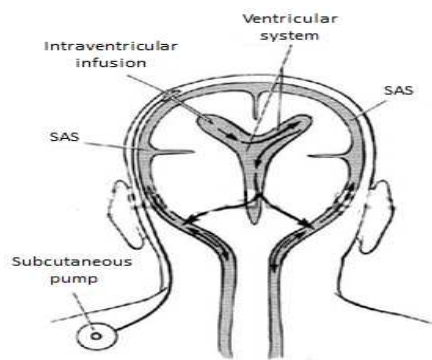
Fig. 4: Intra-ventricular infusion

This result is similar to a slow intravenous infusion rather than a direct administration of drugs into the brain. Pharmacologic effects can be seen after ICV administration, if the target receptors of the drug for example, opioid peptides) are located near the ependymal surface of the brain.

Limitations: The diffusion of the drug in the brain parenchyma is very low. Unless the target is close to the ventricles it is not an efficient method of drug delivery.

2. Convection-enhanced delivery (CED)

The general principle of CED involves the stereotactically guided insertion of a small-caliber catheter into the brain parenchyma. Through this catheter, infusate is actively pumped into the brain parenchyma and penetrates in the interstitial space. The infusion is continued for several days and the catheters are removed at the bedside. CED has been shown in laboratory experiments to deliver high molecular weight proteins 2 cm from the injection site in the brain parenchyma after as little as 2 h of continuous infusion.

Limitations: Some areas of the brain are difficult to saturate fully with infusate, particularly infiltrated tissues surrounding a cavity.

3. Intra-cerebral injection or use of implants

Both the bolus injection of chemotherapy agents and the placement of a biodegradable, chemotherapeutic impregnated, wafer into a tumour resection cavity, rely on the principle of diffusion to drive the drug into the infiltrated brain. Fung et al. (1998) have demonstrated the presence of high drug concentrations (0.5–3.5mMfor carmustine, 0.2–1 mM for paclitaxel) within the first 3 mm from the polymer implants in monkeys; significant concentrations (0.4 μM for carmustine, 0.6 μMfor paclitaxel) were measured up to approx.5 cm from the implant as long as 30 days after implantation.

4. Disruption of the BBB

Disruption of the BBB can open access of the brain to components in the blood by making the tight junction between the endothelial cells of the brain capillaries leaky. Different techniques are used to disrupt the tight junctions:

• Osmotic disruption: The osmotic shock causes endothelial cells to shrink, thereby disrupting the tight junctions. Intracarotid administration of a hypertonic mannitol solution with subsequent administration of drugs can increase drug concentration in brain and tumour tissue to reach therapeutic concentration.

• MRI-guided focused ultrasound BBB disruption technique: Ultrasound has been shown to be capable of BBB disruption. The combination of microbubbles (preformed microbubbles of ultrasound contrast agent, optison, with a diameter of 2–6 μm which is injected into the blood stream before exposures to ultrasound). This technique has been shown to increase the distribution of Herceptin in brain tissue by 50% in a mice model.

• Application of bradykinin-analogue: There is evidence of the opening of the tight junctions to occur by activation of bradykinin B2 receptors through a calcium-mediated mechanism

Limitations of Invasive approach: All these approaches are relatively costly, require anaesthesia and hospitalization, and are non-patient friendly. These techniques may enhance tumour dissemination after successful disruption of the BBB. Neurons may be damaged permanently from unwanted blood components entering the brain.

B) Pharmacological approach

The pharmacological approach to crossing the BBB is based on the observation that some molecules freely enter the brain, e.g. alcohol, nicotine and benzodiazepine. This ability to passively cross the BBB depends on the molecular size being less than 500 D, charge (low hydrogen bonding capabilities) and lipophilicity (the more lipophilic, the better the transport) This approach consists of modifying, through medicinal chemistry, a molecule that is known to be active against a CNS target to enable it to penetrate the BBB. Modification of drugs through a reduction in the relative number of polar groups increases the transfer of a drug across the BBB. Lipid carriers have been used for transport, and there are successful examples of both these approaches. Modification of antioxidants with pyrrolopyrimidines increases their ability to access target cells within the CNS. Enhanced delivery of ganciclovir to the brain was observed by covalently attaching 1-methyl-1, 4-dihydronicotinate to an hydroxymethyl group. Fatty acid such as N-docosahexaenoyl(DHA) have been incorporated in small drugs to increase their brain uptake.

Limitations: The modifications necessary to cross the BBB often result in loss of the desired CNS activity. Increasing the lipophilicity of a molecule to improve transport can also result in making it a substrate for the efflux pump P-glycoprotein (P-gp).

C) Physiological approach

Among all the approaches used for increasing brain delivery of therapeutics, the most accepted method is the use of the physiological approach which takes advantage of the transcytosis capacity of specific receptors expressed at the BBB. The low density lipoprotein receptor related protein (LRP) is the most adapted for such use with the engineered peptide compound (EPiC) platform incorporating the Angiopep peptide in new the most advanced with promising data in the clinic.

Receptor-mediated transcytosis

-Receptors at the blood–brain barrier:

Large molecules which are necessary for the normal function of the brain are delivered to the brain by specific receptors. These receptors are highly expressed on the endothelial cells forming the BBB. These include the insulin receptor, transferrin receptor, LDL receptor and its related protein, and others. Research is still on-going to identify new receptors. The receptor-mediated transcytosis occurs in 3 steps:

1. Receptor-mediated endocytosis of the compound at the luminal (blood) side.

2. Movement through the cytoplasm of the endothelial cell.

3. Exocytosis of the drug at the abluminal (brain) side of the brain capillary endothelium.

The precise mechanism of transcytosis across polarized endothelial cells has not been determined. Additional molecules may be involved in the transcytosis across the BBB and bypassing of lysosomes in the cytoplasm which could degrade the molecules being transported.

The physiologic approach comprises targeting these receptors at the BBB by specific ligands,

modified ligands and antibodies. Therapeutic compounds are able to cross the BBB after association/ conjugation to these specific ligands forming molecular Trojan horses (MTH). To delivery larger amounts of therapeutics liposomes decorated with specific ligand have also been developed

D) Other Non-invasive Approaches

A variety of non-invasive brain drug delivery methods have been investigated, that make use of the brain blood vessel network to gain widespread drug distribution.

Noninvasive techniques usually rely upon drug manipulations which may include alterations as prodrugs, lipophilic analogues, chemical drug delivery, carrier-mediated drug delivery, receptor/vector mediated drug delivery etc.

a) Lipophilic Analogs

CNS penetration is favored by low molecular weight, lack of ionization at physiological pH, and lipophilicity. Delivery of poorly lipid-soluble compounds to the brain requires some way of getting past the BBB. There are several possible strategies, such as transient osmotic opening of the BBB, exploiting natural chemical transporters, highdose chemotherapy, or even biodegradable implants. But all of these methods have major limitations: they are invasive procedures, have toxic side effects and low efficiency, and are not sufficiently safe. Heroin, a diacyl derivative of morphine, is a notorious example that crosses the BBB about 100 times more easily than its parent drug just by being more lipophilic. Hence, a possible strategy is to smuggle compounds across as their lipophilic precursors.Because drug's lipophilicity correlates so strongly with cerebro-vascular permeability, hydrophobic analogues of small hydrophilic drugs ought to more readily penetrate the BBB. This strategy has been frequently employed, but the results have often been disappointing. The best examples of such attempts are the series of lipophilic analogues of nitrosoureas where a quantitative structural activity relationship (QSAR) study indicated the anti-neoplastic activity was inversely proportional to their lipophilicity. This is because the more lipophilic analogs becomes less soluble in the aqueous plasma and bind more readily to plasma proteins, leading to lower concentrations of drug available for diffusion into the CNS and demonstrate diminished alkylating activity and increased dose limiting toxicity. Hence, when a drug is delivered via the circulatory system for the treatment of CNS diseases, a delicate balance between cerebro-vascular permeability and plasma solubility is required. Specifically, the optimal log Po/w is approximately 1.5 to 2.5. However, log Po/w alone seems to have a more limited performance in predicting brain/blood concentration ratios, but in combination with other parameters can still reasonably predict brain-blood partitioning.

A second strategy for increasing the lipophilicity of a hydrophilic therapeutic agent is to surround the hydrophilic molecule with a sphere of lipids in the form of a liposome.

b) Prodrugs

Brain uptake of drugs can be improved via prodrug formation. Prodrugs are pharmacologically inactive compounds that result from transient chemical modifications of biologically active species. The chemical change is usually designed to improve some deficient physicochemical property, such as membrane permeability or water solubility. After administration, the prodrug, by virtue of its improved characteristics, is brought closer to the receptor site and is maintained there for longer

periods of time. Here it gets converted to the active form, usually via a single activating step. For example, esterification or amidation of hydroxy-, amino-, or carboxylic acid- containing drugs, may greatly enhance lipid solubility and, hence, entry into the brain. Once in the CNS, hydrolysis of the modifying group will release the active compound.

Unfortunately, simple prodrugs suffer from several important limitations. Going to extremes on the lipophilic precursor scale, a possible choice for CNS prodrugs is coupling the drug to a lipid moiety, such as fatty acid, glyceride or phospholipids. Such prodrug approaches were explored for a variety of acid-containing drugs, like levodopa, GABA, Niflumic acid, valproate or vigabatrin are coupled to diglycerides or modified diglycerides. While increased lipophilicity may improve movement across the BBB, it also tends to increase uptake into other tissues, causing an increased tissue burden. This selectivity in delivery is especially detrimental when potent drugs such as steroids or cytotoxic agents are considered, since toxicity is exacerbated at nontarget sites. Moreover, while increased lipophilicity may facilitate drug uptake into the CNS, it also enhances efflux processes. This can result in poor tissue retention and short biological action. Furthermore, while the only metabolism associated with a prodrug should be its conversion to the parent drug, other routes can occur, and the formed metabolites may contribute to the toxicity of the compounds. These effects is poor selectivity, poor retention, and the possibility for reactive metabolites, may often conspire to decrease, not to increase, the therapeutic index of drugs masked as prodrugs. On the other hand, prodrug approaches that target specific membrane transporters have also

been explored more recently (chemically) transforming the drug to be delivered so that it can become the subject of some specific membrane transporter, such as the amino acids, peptide or glucose transporters.

b) Receptor/Vector Mediated Drug Delivery

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 chemical linkers, avidin–biotin technology, polyethylene glycol linkers, or liposomes. Multiple classes of therapeutics have been delivered to the brain with the chimeric peptide technology, including peptide- based pharmaceuticals, such as a vasoactive peptide analog or neurotrophins such as brain-derived neurotrophic factor, anti-sense therapeutics including peptide nucleic acids (PNAs), and small molecules incorporated within liposomes. The attachment of the drug that normally does not undergo transport through the BBB to a BBB transport vector such as the MAb, results in the formation of a chimeric peptide, provided the bifunctionalityof the conjugate is retained. That is, the chimeric peptide must have not only a BBB transport function, but also a pharmaceutical function derived from the attached drug. Certain drugs may not be pharmacologically active following attachment to a BBB transport vector. In this case, it may be desirable to attach the drug to the transport vector via a cleavable disulfide linkage that ensures the drug is still pharmacologically active following release from the transport vector owing to cleavage of the disulfide bond. Depending on

the chemistry of the disulfide linker, a molecular adduct will remain attached to the drug following disulfide cleavage, and the molecular adduct must not interfere with drug binding to the drug receptor. A second consideration with respect to the use of a disulfide linker is that virtually all of the cell disulfide reducing activity may be contained within the cytosol. Therefore, the chimeric peptide must undergo endosomal release following receptor-mediated endocytosis into the target brain cell, in order to distribute to the reductase compartment.

A second approach is to attach the drug to the transport vector via a non-cleavable linkage such as an amide bond. In this context, cleavability refers to reduction of the disulfide bond, since all the bonds including amide bonds are ultimately hydrolyzed in the lysosomal compartment. For certain peptide-based therapeutics if (a) a disulfide linker is not desired, and (b) the drug is not biologically active following conjugation via the amide linker, the PEGylation technology is used (Table 1) with a longer spacer arm comprised of a PEG moiety having a molecular mass of 2000–3400. With the PEG linker, the

number of atoms comprising the linker is increased from 14 to _100. The placement of this long spacer arm between the transport vector and the drug releases any steric hindrance caused by attachment of the drug to the transport vector, and drug binding to the cognate receptor is not impaired. These considerations illustrate the multiplicity of approaches for linking drugs to transport vectors (Table 1), and the availability of these multiple approaches allows for designing transport linkers to suit the specific functional needs of the therapeutic under consideration.
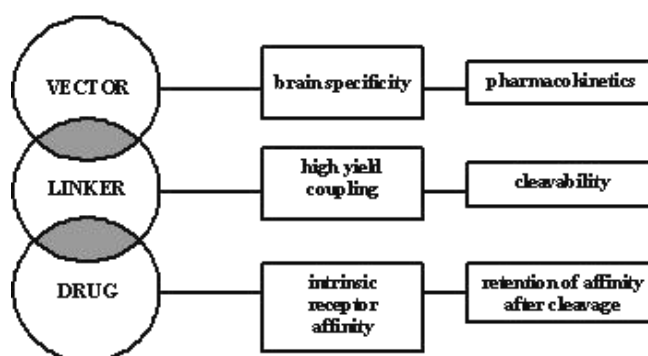

Fig. 5: It shows three interwoven areas of vector, linker and drug development with the corresponding criteria for optimization of each segment

Table 1: Diversity in strategies for linking drugs to transport vectors

CLASS	TARGET AA	AGENT	LINKAGE	CLEAVABILITY
Chemical	Lys	MBS	Thio-ether(-s-)	No
	Lys	Traut's		
	Lys	SPDP	Disulfide(-ss-)	Yes
	Lys	Traut's		
Avidin-Biotin	Lys	NHS-SS-Biotin	Disulfide	Yes
	Lys	NHS-XX-Biotin	Amide	No
	Lys	NHS-PEG-biotin	Extended amide	No
	Asp, Glu	Hz-PEG-biotin	Extended hydrazide	No
Genetic engineering	Fusion gene elements			
	Recombinant protein, recombinant vector			No
	Recombinant vector, recombinant avidin			Flexible

Abbreviations: NHS- N-hydroxy succinimide, PEG-polyethylene glycol, Hz- Hydrazide, MBS- M-maleimidobenzoyl N-hydroxy succinimide Ester, SPDP-N-succinimidyl-3-2-pyridyldithio propionate, Lys-lysine, Asp-Aspartic acid, AA-amino acid.

d) Carrier Mediated Drug Delivery

Carrier-mediated transport (CMT) and receptor-mediated transport (RMT) pathways are available for certain circulating nutrients or peptides. The availability of these endogenous CMT or RMT pathways means that portals of entry to the brain for circulating drugs are potentially available. In the brain capillary endothelial cells, which make up the BBB, there are several transport systems for nutrients and endogenous compounds. They are:

a) The hexose transport system for glucose and mannose,

b) The neutral amino acid transport system for phenylalanine, leucine and other neutral amino acids,

c) The acidic amino acid transport system for glutamate and aspartate,

d) The basic amino acid transport system for arginine and lysine,

e) The b-amino acid transport system for b-alanine and taurine,

f) The monocarboxylic acid transport system for lactate and short-chain fatty acids such as acetate and propionate,

g) The choline transport system for choline and thiamine,

h) The amine transport system for mepyramine,

i) The nucleoside transport system for purine bases such as adenine and guanine, but not pyrimidine bases, and

j) The peptide transport system for small peptides such as enkephalins, thyrotropin-releasing hormone, arginine vasopressin etc.

The promising strategies that can be exploited to promote drug delivery to the CNS are:

- Liposomes targeting to the brain by exploiting receptor mediated transcytosis system,
- Nanoparticles for drug delivery across BBB,
- Implantation within the brain of either genetically engineered cells secreting a drug or a polymeric matrix or reservoir containing the drug,
- Chemical delivery systems based on predictable enzymatic activation,
- Chimeric peptide technology, wherein a non-transportable drug is conjugated to a BBB transport vector,
- Neuroproteomics approaches and gene therapy for CNS disorders[4].

RECENT ADVANCES IN NANO TECHNOLOGY

The research team of University of Michigan has developed a tool to diagnose and treat the most virulent forms of brain cancer.

1. 20-200nm diameter of probes encapsulated by biologically localized embedding (PEBBLES)in brain cancer targeting
2. Chimeric peptide technology
3. Lipobridge technology
4. Peptide radiopharmaceuticals
5. Nanogel, etc.

MAJOR NEEDS IN BRAIN DRUG TARGETING

- Need to target therapeutics to specific brain regions or cell types.
- Need to improve understanding of BBB transport systems.
- Need for in vivo evaluation of brain drug pharmacokinetics.
- Need to identify new brain drug targeting systems.

- Need to speed development and application of molecular imaging probes and targeted contrast agents[7].

Conclusion

The treatment of brain diseases is particularly challenging because the delivery of drug molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the BBB, BCB and BTB. The present outlook for patients suffering from many types of CNS diseases remains poor, but recent developments in drug delivery techniques provide reasonable hope that the formidable barriers shielding the CNS may ultimately be overcome. Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery systems. Substantial progress will only come about, however, if continued vigorous research efforts to develop more therapeutic and less toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to their brain targets.

REFERENCES

1) Garg et al. Challenges of Brain Drug Delivery and G-Technology as One of Solution. J of Pharm and Pharm Sci 2013; 2(3): 13-18.

2) Mohanachandran PS, Sindhumol PG. Recent trends in brain targeting drug delivery system: An overview. International J of Compre Pharm; 3(10): page no. 1-9.

3) Gabathuler R. Approaches to transport therapeutic drugs across the blood–brain barrier to treat brain diseases. J Neurobiology of Disease 2010; 37: 48–57.

4) Misra AN, Ganesh AV, Shahiwala AN. Drug delivery to the central nervous system: a review. J Pharm Pharmaceut Sci 2003; 6(2): 252-273.

5) Bodor N, Buchwald P. Brain-targeted drug delivery: experiences to date. Am J Drug Targ 2003; 1: 13– 26.

6) Pardridge WM. The Blood-Brain Barrier: Bottleneck in Brain Drug Development. The J of the Am Socie for Exptal NeuroTherapeutics; 2(1): 21-29.

7) Pavan P et al. Progress in Drug Delivery to the Central Nervous System by the Prodrug Approach. J of Molecules; 13(5): 1035-1065.

8) Madgulkar AR, Bhalekar MR. Targeted Drug Delivery to CNS using Nanoparticles. J of Adv Pharm Sci 2012; 2(1): 180-191.

9) Soni V, Chorasia MK. Novel approaches for drug delivery to the brain. Indian J. Pharm. Sci. 2004; 66(2): 711-720.

10) Doan KM, Humphreys JE et al. Passive permeability and P-glycoprotein-mediated efflux differentiate central nervous system (CNS) and non-CNS marketed drugs. J Pharm Exp Ther 2003; 303(3): 1029– 1037.

11) Pardridge WM. Recent advances in blood brain-barrier transport. *Annu Rev Pharmacol Toxicol* 1988; 28: 25-39.

12) Cornford EM, Braun LD, Oldendorf WH. Comparison of lipid-mediated blood–brain barrier penetrability in neonates and adults. *Am J Physiol* 1982; 243(3): C161–C168.

13) 13) Siegal E, zylber-Katz E. Strategies for increasing drug delivery to the brain: focus on brain lymphoma. *Clin Pharmacokinet* 2002; 41: 171-186.

14) Yoshikawa T, Pardridge WM. Biotin delivery to brain with a covalent conjugate of avidin and a monoclonal antibody the transferring receptor. *J Pharmacol Exp Ther* 1992; 263(2): 897–903.

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