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# BRAIN DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW ON RECENT EXPERIMENTAL AND CLINICAL FINDINGS

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**Keywords:**

Blood brain barrier (BBB), Endogenous transporters, Novel drug delivery system, Carrier mediated transport, Receptor mediated transport, BBB-disruption

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## ABSTRACT

The blood- brain barrier (BBB) denies many therapeutic agents access to brain tumors and other diseases of the central nervous system (CNS). Despite remarkable advances in our understanding of the mechanisms involved in the development of the brain diseases and the actions of neuroactive agents, drug delivery to the brain remains a challenge. For more than 20 years, extensive efforts have been made to enhance delivery of therapeutic molecules across vascular barriers of the CNS. BBB allows a selective entry of nutrients and minerals across it and limits the entry of foreign substances like drugs as well as neuropharmaceutical agents. This makes the CNS treatment ineffective. The conventional drug delivery systems which release drug into general circulation fail to deliver drugs effectively to brain and is therefore not very useful in treating certain diseases that affect CNS including Alzheimer's disease, dementia, Parkinson's disease, mood disorder, AIDS, viral and bacterial meningitis. The current challenge is to develop drug delivery strategies that will allow the passage of drug molecules through the BBB in a safe and effective manner. The present review enlightens recent experimental and clinical findings in brain drug targeting that would give an insight to the researchers, academia and industrialists.

**INTRODUCTION:** It is estimated that about 1.5 billion people worldwide are suffering from some type of central nervous system (CNS) disorder. Therefore, there is a strong demand from patients for effective treatments. These numbers will substantially increase over the next decades due to an increasing number of elderly people in the general population. The number of people with CNS disorders will be approximately 1.9 billion by 2020, unless concerted action is undertaken to stem this toll [1]. The blood-brain barrier (BBB) is single most important factor limiting the future growth of neurotherapeutics. The BBB represents a very complex endothelial interface in vertebrates which separates the blood compartment from the extracellular fluid compartment of the brain parenchyma (**Fig. 1**). The BBB consists of a monolayer of polarized endothelial cells connected by complex tight junctions. It is a continuous zipper-like tight junctioned endothelial cellular layer [2].

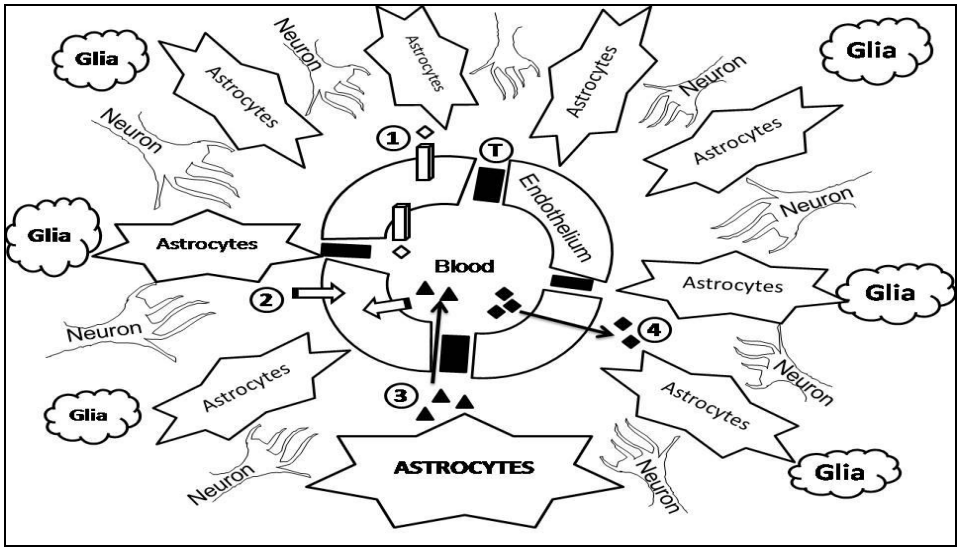


**FIG. 1: THE MAJOR PATHS FOR THE TRANSPORT OF MOLECULES ACROSS THE BBB ARE SHOWN. (1) TRANSPORT PROTEINS: THE ENDOTHELIAL CELLS CONTAIN CARRIER PROTEINS FOR CHOLINE, AMINO ACIDS, GLUCOSE, PURINE BASES, NUCLEOSIDES, ETC. (2) RECEPTOR MEDIATED TRANSCYTOSIS (3) PARACELLULAR PATHWAY (4) TRANSCELLULAR PATHWAY (5) RECEPTOR MEDIATED TRANSCYTOSIS, T: TIGHT JUNCTIONS**

The luminal plasma membrane of the endothelial cells faces the blood compartment, whereas the abluminal membrane is directed towards the brain extracellular fluid. Among the crucial properties of BBB endothelia is the capacity to act as a mainly selective barrier, thus isolating the brain from systemic influences, while simultaneously providing a pathway for the transport of nourishment to neurons buried in the brain parenchyma. In addition, the process of clearance of potentially toxic substances from the brain into the blood also relies on BBB-related mechanisms. Because of the efficiency with which the BBB performs its defensive function, the treatment of brain cancer and other neurodegenerative diseases has been relatively inefficient because many drugs are unable to reach the brain at the necessary therapeutic levels [3]. Unlike peripheral capillaries that allow relatively free exchange of substance across cells, the BBB rigorously limits transport into the brain. BBB not only functions as a physical barrier, but also a biochemical barrier that expresses certain enzymes like peptidases along with several cytosolic enzymes and efflux p-glycoprotein system that helps effluxing drugs from the endothelial cells back into the blood which helps in its further protecting action towards the brain microenvironment [4]. Thus the BBB is often the rate-limiting factor in determining permeation

of therapeutic drugs into the brain. Transport kinetic, metabolic, cellular and molecular studies have given a major impetus to an improved understanding of how the BBB functions, and how this can be exploited in therapeutic terms [5].

The present review enlightens not only the basic physiology of BBB, Drug delivery strategies, Transporters/ Carriers but also the recent experimental and clinical findings in brain drug targeting that would give an insight to the researchers, academia and industrialists.

**BBB & Drug Delivery to the Brain:** The BBB drug delivery problem can be solved, but this requires new approaches to this area of pharmaceutics. The old ways of drilling a hole in the head for trans-cranial brain drug delivery, or medicinal chemistry attempting to lipidize a water-soluble small molecule, must give way to new approaches. The new technology is based on knowledge of endogenous BBB transporters, and aims to reformulate drug structures so that these molecules can cross the BBB via endogenous transport systems. This is a radical departure from existing practices in CNS drug development. However, unless changes are made, the future of CNS drugs will be limited to the small class of drugs that cross the BBB via lipid-mediated free diffusion: lipid-soluble small molecules with a molecular weight (MW) <400 Da. These drugs treat only a handful of CNS conditions, generally restricted to affective disorders, epilepsy and insomnia [6].

A common misconception is that small molecules readily cross the BBB. However, in fact, >98% of all small molecules do not cross the BBB either. There are >7000 drugs in the Comprehensive Medicinal Chemistry (CMC) database, and only 5% of these drugs treat the CNS, and the drugs that do treat the CNS are limited to treatment of just three conditions: depression, schizophrenia and insomnia. It has been investigated that 100% of large molecule drugs and 98% of small molecule drugs do not cross BBB [7]. For a small molecule drug to cross the BBB in significant amounts, the molecule must have two important characteristics like molecular mass must be under 400 Da and high lipid solubility [8]. Due to these reasons the brain drug targeting becomes more difficult for the pharmaceutical industries. Several strategies have been investigated (**Fig. 2**) for effective clinical outcome for different CNS conditions. A brief account on drug molecules being used by several approaches for brain targeting has been summarized in **table 1**.

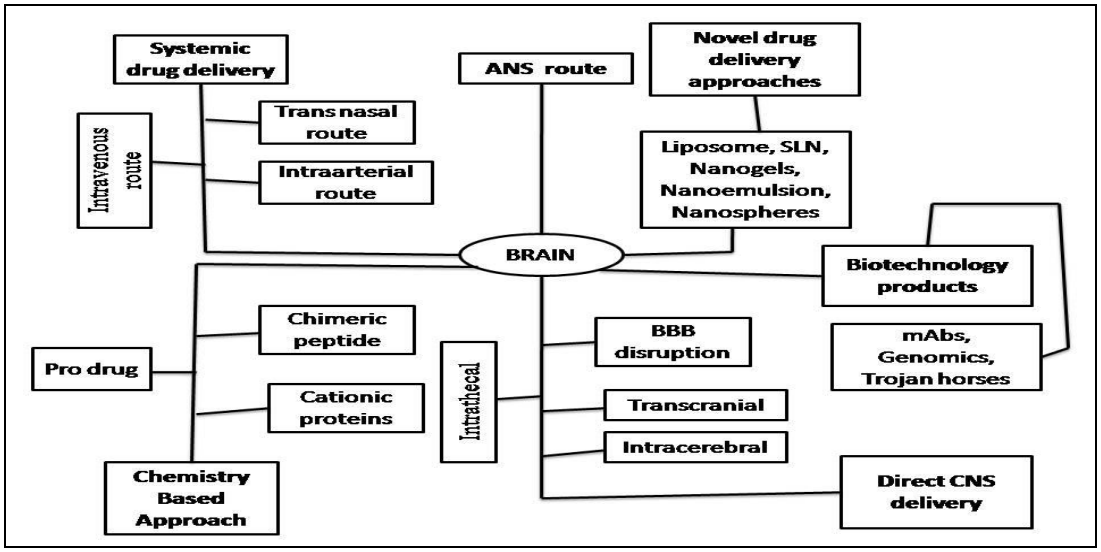


**FIG. 2: OVERVIEW OF DIFFERENT APPROACHES OF BRAIN TARGETING; (ANS- AUTONOMIC NERVOUS SYSTEM; CNS- CENTRAL NERVOUS SYSTEM; BBB- BLOOD BRAIN BARRIER; MABS- MONOCLONAL ANTIBODIES)**

**TABLE 1: BRIEF ACCOUNT ON DRUG MOLECULES BEING USED BY SEVERAL APPROACHES FOR BRAIN TARGETING**

| DRUG | PROBLEM | APPROACH | INFERENCE |
|---|---|---|---|
| Dopamine, Morphine | High water solubility and lower lipid solubility | Transnasal route | Observed satisfactory cerebral concentration due to crossing of olfactory CSF through nasal mucosa and get available into general CSF |
| NAD+ (antioxidant co-factor) | --- | Intranasal route | Decreased brain injury in a rat model of transient focal ischemia |
| Gallotannin (a PARG inhibitor) | --- | Intranasal route | Decreased frequency of ischemic brain injury in rats |
| Olanzapine (antipsychotic agent) | Lesser uptake drug due to hydrophobicity | Given in microemulsion formulation containing mucoadhesive polymer intranasally | Significantly higher concentration achieved in brain microenvironment due to increased solubility and mucoadhesive nature |
| Cytosine arabinoside (an anticancer agent) | --- | Given by intracerebral injection | Results showed superior cerebral blood level as compared to intraventricular, transnasal and i.v. route due to convection enhanced diffusion |
| GDNF (glial derived neurotropic factor) (for treating parkinsonism) | Difficult to administer by any other route due to its deviation from cerebrospinal fluid flow tracts | Administered via Intra cerebroventricular injection | Achieved better cerebral concentration to treat parkinsonism |
| Cytosine arabinoside (for treating neoplastic meningitis) | Rapid turnover from cerebral environment due to leakage of CSF and lower half life | Given in a suspension formulation containing multivesicular lipid “DepoCyt” of size 3- 30Am intraventricularly | Observation showed increased half life of drug from 0.74 to 156 hrs with sustained release profile of drug delivery |
| Etoposide (for treating metastatic brain tumors) | Drug shows lesser concentration in brain | Instigated in the form of reservoir type osmotic pump (Omayama, Mini Med PIMS system, Medtronic Synchro Med system osmotic systems) by implantation | Showed 100-fold much effective concentration as earlier |
| Lomustine (BCNU). (anticancer) | Due to lower residence time of the drug in cerebral microenvironment due to leakage by ISF | Give in the form of a monolithic or matrix based depot preparation injected into brain micro blood vessels | Satisfactory cerebral concentration of drug was achieved by slow diffusion of drug from depot site into brain cells by active transport from endothelial cells approximately upto 6 weeks |
| Dalargin, Kyotorphin (analgesic) | Due to high molecular weight these peptides are unable to cross junctional BBB | Peptides are given in poly butyl cyanoacrylate nanoparticles coated with polysorbate-80 to protect from opsonisation | Considerable cerebral peptide concentration achieved with decreased frequency of algesic attacks |
| Doxorubicin | --- | Given in the form of nanoparticle system which is coated polysorbate-80. | Because of very small size nano particles travelled in brain intact by releasing the drug in brain micro environment directly and due to endocytotic uptake |

**BBB- Carrier mediated transport (BBB-CMT):** The CMT systems shown in **Figure 3** are all members of the Solute Carrier (SLC) gene family. The BBB glucose carrier is GLUT1 (glucose transporter type 1), which is a member of the SLC2 family; the BBB monocarboxylic acid transporter is MCT1, which is a member of the SLC16 family; the BBB large neutral amino acid and cationic amino acid transporters are LAT1 and CAT1, respectively, which are members of the SLC7 family; LAT1 and CAT1 are the light chains of heterodimeric proteins, and the heavy chain of the dimer is 4F2hc, which is a member of the SLC3 family; the BBB adenosine transporter is CNT2, which is a member of the SLC28 family (**table 2 & 3**).

Each of the SLC families represents many common genes of overlapping nucleotide identity and some of the SLC families are comprised of over 100 different genes. BBB GLUT1 transports glucose, 2-deoxyglucose, 3-*O*-methyl-glucose, galactose, and mannose, but not Lglucose [9]. BBB MCT1 transports lactate, pyruvate, ketone bodies, and monocarboxylic acids [10] BBB LAT1 transports the neutral amino acids with preferential affinity for the large neutral amino acids [11] BBB CAT1 transports arginine, lysine, ornithine [12]. The BBB choline transporter transports choline, and perhaps other quaternary ammonium molecules [13]. To date, the BBB choline transporter has not been cloned.

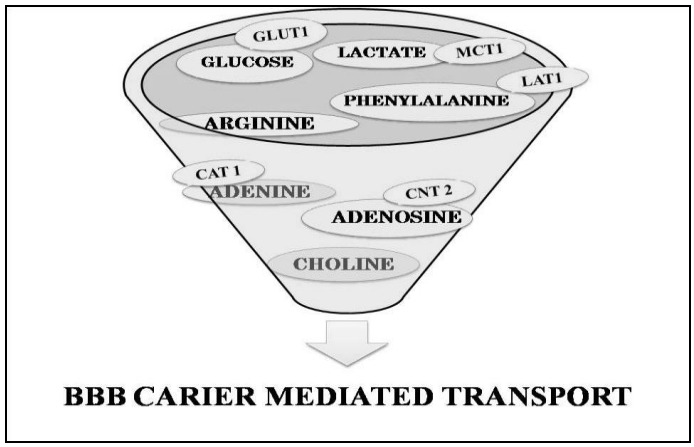


**FIG. 3: BBB CMT SYSTEMS ARE SHOWN FOR SEVEN DIFFERENT CLASSES OF NUTRIENTS AND THE GENES FOR FIVE OF THESE SYSTEMS HAVE BEEN IDENTIFIED. GLUT1= GLUCOSE TRANSPORTER TYPE 1; MCT1= MONOCARBOXYLIC ACID TRANSPORTER TYPE 1; LAT1 = LARGE NEUTRAL AMINO ACID TRANSPORTER TYPE 1; CAT1 = CATIONIC AMINO ACID TRANSPORTER TYPE 1; CNT2 = CONCENTRATIVE NUCLEOSIDE TRANSPORTER TYPE 2**

In addition to the CMT systems shown in Figure 3, there are many other CMT genes expressed at the BBB, which enable the BBB transport of water-soluble vitamins, thyroid hormones, and other compounds. All of these CMT systems at the BBB, which may number in the dozens, are potential portals of entry of drugs to the brain. The CMT systems comprise highly stereo specific pore-based transporters, and there are significant structural requirements for transporter affinity. Therefore, it is unlikely that a drug, which is normally not transported across the BBB, would be made transportable by simply coupling to the drug to another molecule that undergoes CMT across the BBB. Rather, the structure of the pharmaceutical should be altered with medicinal chemistry so that it takes on the structure of a pseudo-nutrient and thus is able to undergo transport across the BBB via one of the CMT systems (**fig. 4**).

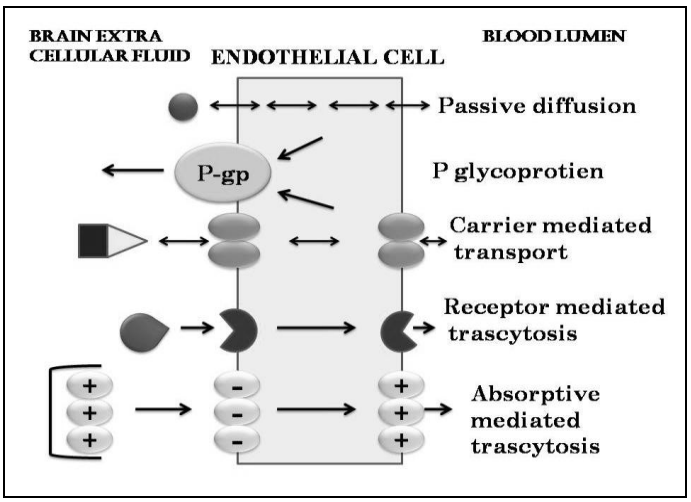


**FIG. 4: TRANSPORT MECHANISMS ACROSS THE BLOOD- BRAIN BARRIER (BBB).**

The mechanisms that play an important role in crossing the bbb are: passive diffusion, which depends mainly on the lipophilicity of the molecule; p-glycoprotein (p-gp), an atp-dependent protein that acts as an efflux pump; carrier-mediated transport that uses specific carrier systems; and transcytosis, either via a receptor (receptor-mediated) or via electrostatic interactions (absorptive-mediated)

**TABLE 2: DESCRIPTION OF RECEPTORS RESPONSIBLE FOR THE TRANSPORT OF MOLECULES THROUGH BBB**

| Transport system | Receptors | Molecules |
|---|---|---|
| **Receptor mediated transport (RMT)** | Insulin receptor (INSR) | Insulin |
| | Transferring receptor (TFR) | Transferrin |
| | Insulin-like growth factor receptors (IGF1R & IGF2R) | Insulin like growth factor 1 & 2 (IGF-1& IGF-2), mannose-6-phosphate |
| | Lectin receptor (LEPR) | Lectin |
| | Fc like growth factor receptor(FCGRT) | IgG |
| | Scavenger receptor type B1 (SCARB1) | Modified lipoproteins, like acetylated low density lipoprotein (LDL) |

**TABLE 3: DESCRIPTION OF CARRIER MEDIATED TRANSPORT SYSTEM WITH DIFFERENT TRANSPORTERS AND ENDOGENOUS MOLECULES TO BE TRANSPORTED**

| Transport system | Transporters | Molecules | Use |
|---|---|---|---|
| **Carrier mediated transport (CMT)** | GLUT1 (Glucose transporter 1) | Glucose, hexose, 2-deoxyglucose, fluorodeoxy glucose | Positron emission tomography (PET) scanning |
| | LAT1 (Large neutral amino acid transporter 1) | Large and small neutral amino acids, L-dopa (Levodopa), -α-methyl-dopa (Methyldopa), α-methyl-para-tyrosine or gabapentin | In parkinsonism, hypertension and in delivery of antiepileptic drugs |
| | CAT1 (Cationic amino acid transporter 1) | Basic amino acids, like arginine or lysine | ----- |
| | MCT1 (Monocarboxylic acid transporter 1) | Lactate, pyruvate, ketone bodies and monocarboxylic acid drugs like probenecid | In treatment of gout and urinary incontinence |
| | CNT2 (Concentrative nucleoside transporter 2) | Purine nucleosides, and certain pyrimidine nucleosides as uridine | In delivery of several anticancer and antiviral drugs |
| | SLCs (Choline transporter) (Sodium dependent) | Choline | A cholinergic agent used in experimental techniques, not as a drug |

**Blood-Brain barrier disruption:** In parallel with trans-cranial brain drug delivery strategies, there has been a significant effort in delivering drugs to the brain with BBB disruption after the intracarotid arterial infusion of vasoactive agents. The intracarotid arterial infusion of 2 M concentrations of poorly diffusible solutes such as mannitol causes disruption of the BBB owing to osmotic shrinkage of the endothelial cells [14]. This is associated with severe vasculopathy [15] and chronic neuropathologic changes in rodent models [16] and is also associated with seizures in either animal models [17] or humans [18]. Plasma proteins such as albumin are toxic to brain cells and BBB disruption allows for the uptake of plasma into the brain.

An alternative explanation is that the drug is injected in a diluent that is membrane destabilizing, and causes BBB disruption. Often the drug is solubilized in solvents such as ethanol or DMSO (Dimethyl sulfoxide), or surfactants such as SDS, a Tween detergent, or other surfactants, such as polyethyleneglycol hydroxyl stearate. Doses of solvents such as ethanol or DMSO at a level of 1-4 g/kg may cause solvent-mediated disruption of the BBB [19, 20]. This dose of DMSO or ethanol is given to animal models with surprising frequency, particularly small rodent models such as mice, which weigh only 20-30 g. The administration of just 50 µl of 50% DMSO to a 20-g mouse is equivalent to 1.25 g/kg DMSO, and there are examples in the

literature of pharmacologic effects achieved in brain following systemic administration of drugs that normally do not cross the BBB. These drugs are administered in solvents such as ethanol or DMSO and the dose of solvent is such that BBB disruption may be caused by administration of the drug/solvent mixture. Tween 80, also known as polysorbate-80, is frequently administered in CNS drug formulations. A dose of polysorbate-80 of 3-30 mg/kg will cause BBB disruption in mice [21].

Analgesia with kyotorphin, a oligopeptide that normally does not cross the BBB, is possible following the peripheral administration of the peptide, providing Tween 80 is co-administered [22]. Low doses of another surfactant, SDS, are frequently included in CNS drug diluents. However, doses of SDS as low as 1.0 µg/kg can cause disruption of the BBB for short periods. Immune adjuvants such as Freund's complete or incomplete adjuvant cause disruption of the BBB to circulating IgG that can persist for weeks [23].

**Trans-cranial brain drug delivery:** Trans-cranial brain drug delivery approaches attempt to bypass the BBB using one of three neurosurgical based delivery approaches: intracerebral implantation, intracerebroventricular (ICV) infusion, and convection enhanced diffusion (CED). The factor limiting either the intracerebral or ICV infusion approach is that either method relies on diffusion for drug penetration into the brain from the depot site. Solute diffusion decreases with the square of the diffusion distance [1].

Therefore, the concentration of drug decreases logarithmically with each millimeter of brain tissue that is removed from the injection site, in the case of intracerebral implantation, or from the ependymal surface of the brain, in the case of ICV infusion. The concentration of a small molecule is decreased by 90% at a distance of only 0.5 mm from the intracerebral implantation site in rat brain [24]. The logarithmic decrease in drug concentration from the ependymal surface following an ICV infusion was shown in the 1970s in adult Rhesus monkeys; after ICV drug injection, the concentration of small molecules in brain parenchyma removed only 1-2 mm from the ependymal surface is only about 1-2% of the concentration in the CSF compartment [25]. The ICV injection of drug should be regarded as a slow intravenous infusion rather than a direct administration of drug into the brain [26]. The rapid rate of cytokine distribution into blood, but minimal penetration into brain, following an ICV injection has been demonstrated in adult rhesus monkeys [27].

The effective penetration of drug into brain can be increased to a treatment radius of a few millimeters when bulk flow is used to deliver drug into brain parenchyma, and this is possible by forcing fluid through the brain with CED. However, the brain has no lymphatic system and is not designed for a significant intraparenchymal volume flow. CED in humans with glioblastoma multiform causes a preferential flow of the forced fluid along white matter tracts [28]. CED in the adult Rhesus monkey brain with glial-derived neurotropic factor involved the infusion of relatively small volumes of ≈0.1 ml/day over a 4-week period [29].

**Trans-nasal drug delivery to the brain:** The respiratory region of the nose is considered to be the major site for drug absorption into the systemic circulation, where the compounds can be absorbed by transcellular pathways or paracellular passive absorption, carrier-mediated transport, and absorption through transcytosis pathways. The olfactory region, next to respiratory region, is the foremost site from where drug can be absorbed directly into the brain by different mechanisms including transcellular, paracellular, olfactory and trigeminal neural pathways [30]. The olfactory region of nasal mucosa contains olfactory cells which extend up into cranial cavity. When the drug

formulation on nasal installation, comes in contact with the mucosa they are rapidly transported directly into the brain, skipping the BBB, and achieving very rapid cerebrospinal fluid levels [31, 32].

Most of the lipid soluble molecules can readily enter the blood stream from the nasal mucosa and subsequently reach the CNS by crossing the BBB.[33] But majority of the pharmaceutical drug molecules are hydrophilic, which becomes another rate limiting barrier for drug targeting, as highly lipid soluble drug molecules show easier and better targeting ability due to higher partition coefficient. It has been reported that the drugs other than lipid soluble molecule can cross nasal mucosa if there is a local injury as that can lead to breakdown of the nasal mucosal barrier [34]. In the recent years several drugs as well as peptides have been delivered effectively using intranasal route. Administration of NAD+ greatly decreased brain injury in a rat model of transient focal ischemia and profoundly decreased oxidative cell death [35].

Similarly intranasal administration of gallotannin, a poly (ADP-ribose) glycohydrolase (PARG) inhibitor showed a marked reduction in the frequency of ischemic brain injury in rats.[36] Olanzapine when delivered intranasally as mucoadhesive microemulsion formulation showed better effectiveness of the route of drug delivery into brain [37, 38]. The delivery of buspirone hydrochloride as mucoadhesive formulation using chitosan and hydroxylpropyl beta cyclodextrin showed better brain concentration after intranasal administration in mice [39]. Similarly intranasal mucoadhesive microemulsion of sumatriptan showed better cerebral concentration and reduction in migraine headache [40].

**Intravenous drug delivery to the brain:** Structurally the surface area of brain constitutes spreading of the network of capillaries with an approximately 20$m^2$ areas; hence the drug delivery approach through transvascular route helps better in brain drug targeting. As the neurons in brain are well connected with the blood vessels, the delivered drug can get access to brain crossing the vascular barrier [41], and therefore this approach is considered to have great potential to deliver drugs to almost all neurons in brain.

However, there is little accumulation of the drug in the brain because of the BBB and rapid clearance from the ECF (extracellular fluid). In addition, the brain availability of drug through IV route is largely affected by the half life of the drug in the plasma, rapid metabolism, level of non-specific binding to plasma proteins and the permeability of the compound across the BBB and into peripheral tissues [42]. The gene expression was found to be effective when delivered through intravenous injection from the external source into brain and exhibited high level of expression in all neurons [43, 44].

The outcome of the route was found to be quite effective in delivery of drugs to brain when administered using a suitable carrier system like polymeric depots, liposomes or lipid carriers. Doxorubicin when administered intravenously using polysorbate 80-coated nanoparticles exhibited 40% cure in rats with intracranially transplanted glioblastomas 101/8 [45]. Several other drugs like the hexapeptide Dalargin [46] loperamide [47], Tubocurarine [48] have been successfully delivered to the brain using polysorbate 80-coated nanoparticles intravenously.

**Intracerebral (intraparenchymal) drug delivery to the brain:** Intracerebral delivery involves delivery of drug directly into parenchymal space of the brain.[49] Drugs can be injected directly (bolus or infusion) via intrathecal catheters, by controlled release matrices [50], microencapsulated chemicals [51] or recombinant cells [52]. The major problem with bolus injection is slower movement of compounds within the brain

due to the limited diffusion coefficient. The reason is due to the closely packed arrangement of cells in both gray as well as white matter microenvironment and due to the concentration dependent diffusion phenomena in brain [53]. Hence a large amount of dose is required for an appropriate drug concentration in parenchyma [54].

Alternatively the continuous infusion method can be used which uses convection enhanced diffusion (CED) phenomena to drive the drugs to a larger tissue region. It has been found that in comparison to bolus injection the CED has better ability to deliver the drug in large doses, maintaining drug concentration and distribution over time [55]. Intracerebral implants are devices for controlled release of drugs at the target site in the brain. Implants are made up of biodegradable/non-biodegradable polymeric materials encapsulating drugs inside it. The basic mechanism behind drug release from these devices is diffusion. Several examples of this approach are available where brain implants have already been used for curing diseases. An implant containing nerve growth factor when placed in brain to treat a quadriplegic patient showed better results from spinal cord damage [56, 57]. These implants are placed inside the brain surgically where they release the drug for a predetermined level of time.

**RECENT EXPERIMENTAL AND CLINICAL FINDINGS:**

1. **Beata Chertok *et al.*** [58]: This study aimed to examine the applicability of polyethyleneimine (PEI)-modified magnetic nano- particles (GPEI) as a potential vascular drug/gene carrier to brain tumors. In vitro, GPEI exhibited high cell association and low cell toxicity properties which are highly desirable for intracellular drug/gene delivery. In addition, a high saturation magnetization of 93emu/g Fe was expected to facilitate magnetic targeting of GPEI to brain tumor lesions. However, following intravenous administration, GPEI could not be magnetically accumulated in tumors of rats harboring orthotopic 9L-gliosarcomas due to its poor pharmacokinetic properties, reflected by negligibly low plasma AUC of 12±3mg Fe/ml min. To improve “passive” GPEI presentation to brain tumor vasculature for subsequent “active” magnetic capture, we examined the intra-carotid route as an alternative for nanoparticle administration. Intra-carotid administration in conjunction with magnetic targeting resulted in 30-fold (p¼ 0.002) increase in tumor entrapment of GPEI compared to that seen with intravenous administration. In addition, magnetic accumulation of cationic GPEI (z-potential¼þ 37.2mV) in tumor lesions was 5.2-fold higher (p ¼ 0.004) than that achieved with slightly anionic G100 (z-potential¼_12mV) following intra-carotid adminis- tration, while no significant accumulation difference was detected between the two types of nano- particles in the contra-lateral brain (p ¼ 0.187).

2. **N. Vykhodtseva *et al.*** [59, 60]: Microbubbles are fine gas bubbles of less than 50µm in diameter. When exposed to ultrasound, these microbubbles serve as the cavitation nuclei to focus and transduce the acoustic energy into mechanical power. Studies have shown that this combinational approach was able to induce transient disruption of the BBB. This may lead to enhanced delivery of therapeutic compounds into the brain compartment. However, there are several concerns regarding the safety of this strategy. More work is required to establish the optimal conditions for extensive use of this method.

3. **William M. Pardridge** [7]: Neuropharmaceutics is the largest potential growth sector of the pharmaceutical industry. However, this growth is blocked by the problem of the blood–brain barrier (BBB). Essentially 100% of large-molecule

drugs and >98% of small-molecule drugs do not cross the BBB. The BBB can be traversed because there are multiple endogenous transporters within this barrier. Therefore, brain drug development programs of the future need to be re-configured so that drugs are formulated to enable transport into the brain via endogenous BBB transporters.

4. **Ho Lun Wong *et al.*** [61]: Once in the brain compartment the virus actively replicates to form an independent viral reservoir, resulting in debilitating neurological complications, latent infection and drug resistance. Current antiretroviral drugs (ARVs) often fail to effectively reduce the HIV viral load in the brain. This, in part, is due to the poor transport of many ARVs, in particular protease inhibitors, across the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSBF).

   Studies have shown that nanocarriers including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLN) and micelles can increase the local drug concentration gradients, facilitate drug transport into the brain via endocytotic pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites. By delivering ARVs with nanocarriers, significant increase in the drug bioavailability to the brain is expected to be achieved. Recent studies show that the specificity and efficiency of ARVs delivery can be further enhanced by using nanocarriers with specific brain targeting, cell penetrating ligands or ABC-transporters inhibitors.

5. **Kullervo Hynynen *et al.*** [62]: Noninvasive, transient, and local image-guided blood-brain barrier disruption (BBBD) has been demonstrated with focused ultrasound exposure in animal models. Most studies have combined low pressure amplitude and low time average acoustic power burst sonication with intravascular injection of pre-formed micro-bubbles to produce BBBD without damage to the neurons. The BBB has been shown to be healed within a few hours after the exposure. The combination of focused ultrasound beams with MR image guidance allows precise anatomical targeting as demonstrated by the delivery of several marker molecules in different animal models. Most notably, the delivery of the chemotherapy agents (liposomal Doxorubicin and Herceptin) has been shown in a rat model.

6. **Aneesh B. Singhal *et al.*** [63]: In addition to these normal restrictions to brain drug delivery, pathophysiological features and sequel of acute brain injury will also impact upon the efficiency of drug delivery. Pathophysiological events that may influence drug delivery include blood–brain barrier disruptions, blood flow alterations, edema and increased intracranial pressure, metabolic perturbations, and altered profiles of gene expression and protein synthesis. Careful consideration of these obstacles will provide a framework for further research into the optimization of drug delivery strategies into damaged brain. Without a rigorous assessment of these issues, it may not be possible to translate our mechanistic understanding of acute brain injury into successful clinical therapies.

7. **Grace H. Huynh *et al.*** [64]: Brain tumor patients face a poor prognosis despite significant advances in tumor imaging, neurosurgery and radiation therapy. Potent chemotherapeutic drugs fail when used to treat brain tumors because biochemical and physiological barriers limit drug delivery into the brain. In the past decade a number of strategies have been introduced to increase drug delivery into the brain parenchyma. In particular, direct drug administration into the brain tumor has shown

promising results in both animal models and clinical trials. This technique is well suited for the delivery of liposome and polymer drug carriers, which have the potential to provide a sustained level of drug and to reach cellular targets with improved specificity.

8. **Chee Seng Teo *et al.*** [65]: The coupled mass and momentum equations are solved for the steady-state solutions of the pressure and velocity distributions at a cut section of a tumor. The steady-state solution thus obtained is then perturbed to compute the characteristic time scale of the variation in the interstitial fluid pressure and velocity in a surgical cavity immediately after surgery. Simulation results show that the flow field reaches an equilibrium state in less than 3 h.

   The surgery produces a transient enhancement of the drug delivery but the surgery alone is not capable of removing permanently the unfavorable pressure gradient against the delivery of drug to tumor. The presence of post-surgery edema increases the interstitial pressure and fluid velocity, thus causing higher relative toxicity in the surrounding normal tissues. Simulations employing complete 3D structure show qualitatively similar results with 2D simulation and hence the use of a cut section of the tumor for simplified model calculations is validated.

9. **Alpesh Mistry *et al***. [66]: Experiments in animal models have shown that nano-sized drug delivery systems can enhance nose-to-brain delivery of drugs compared to equivalent drug solutions formulations. Protection of the drug from degradation and/or efflux back into the nasal cavity may partly be the reason for this effect of nanoparticles. It is uncertain, however, whether drug from the nanoparticles is being released in the nasal cavity or the nanoparticles carrying the drug are transported via the olfactory system or the trigeminal nerves into the CNS where the drug is released. Furthermore, toxicity of nanoparticulate drug delivery systems in the nasal cavity and/or in the CNS has not been extensively studied and needs to be considered carefully.

10. **Celeste Roney *et al.*** [67]: Alzheimer's disease (AD) is the most common cause of dementia among the elderly, affecting 5% of Americans over age 65, and 20% over age 80. An excess of senile plaques (h-amyloid protein) and neurofibrillary tangles (tau protein), ventricular enlargement, and cortical atrophy characterizes it. Unfortunately, targeted drug delivery to the central nervous system (CNS), for the therapeutic advancement of neurodegenerative disorders such as Alzheimer's, is complicated by restrictive mechanisms imposed at the blood–brain barrier (BBB). Opsonization by plasma proteins in the systemic circulation is an additional impediment to cerebral drug delivery. Biodegradable polymeric nanoparticles (NPs) with appropriate surface modifications can deliver drugs of interest beyond the BBB for diagnostic and therapeutic applications in neurological disorders, such as AD.

11. **Mukesh Kumar *et al.*** [68]: The objective of investigation was to prepare nanoemulsion containing risperidone (RSP) to accomplish the delivery of drug to the brain via nose. Risperidone nanoemulsion (RNE) and mucoadhesive nanoemulsion (RMNE) were characterized for drug content, pH, percentage transmittance, globule size and zeta potential. Biodistribution of RNE, RMNE, and risperidone solution (RS) in the brain and blood of Swiss albino rats following intranasal (i.n.) and intravenous (i.v.) administration was examined using optimized technetium labeled (99mTc-labeled) RSP formulations. Gamma scintigraphy

imaging of rat brain following i.v. and i.n. administrations were performed to ascertain the localization of drug in brain. The brain/blood uptake ratio of 0.617, 0.754, 0.948, and 0.054 for RS (i.n.), RNE (i.n.), RMNE (i.n.), and RNE (i.v.), respectively, at 0.5 h are indicative of direct nose to brain transport bypassing the blood–brain barrier. Higher drug transport efficiency (DTE%) and direct nose to brain drug transport (direct transport percentage, DTP%) for mucoadhesive nanoemulsions indicated more effective and best brain targeting of RSP amongst the prepared nanoemulsions. Studies conclusively demonstrated rapid and larger extent of transport of RSP by RMNE (i.n.) when compared to RS (i.n.), RNE (i.n.) and RNE (i.v.) into the rat brain.

12. **Wei Lu *et al.*** [69]: A novel drug carrier for brain delivery, cationic bovine serum albumin (CBSA) conjugated with poly (ethyleneglycol)–poly (lactide) (PEG–PLA) nanoparticle (CBSA–NP), was developed and its effects were evaluated. The copolymers of methoxy-PEG–PLA and maleimide-PEG–PLA were synthesized by ring opening polymerization of d,l-lactide initiated by methoxy-PEG and maleimide-PEG, respectively, which were applied to prepare pegylated nanoparticles by means of double emulsion and solvent evaporation procedure.

    Native bovine serum albumin (BSA) was cationized and thiolated, followed by conjugation through the maleimide function located at the distal end of PEG surrounding the nanoparticle's surface. To evaluate the effects of brain delivery, BSA conjugated with pegylated nanoparticles (BSA–NP) was used as the control group and 6-coumarin was incorporated into the nanoparticles as the fluorescent probe. The qualitative and quantitative results of CBSA–NP uptake experiment compared with those of BSA–NP showed that rat brain capillary endothelial cells (BCECs) took in much more CBSA–NP than BSA–NP at $37^0$C, at different concentrations and time incubations. After a dose of 60 mg/kg CBSA–NP or BSA–NP injection in mice caudal vein, fluorescent microscopy of brain coronal sections showed a higher accumulation of CBSA–NP in the lateral ventricle, third ventricle and periventricular region than that of BSA–NP. There was no difference on BCECs' viability between CBSA-conjugated and -unconjugated pegylated nanoparticles.

13. **Lihong Liu *et al***. [70]: Biologically active polymer core/shell nanoparticles (i.e. micelles) self-assembled from TATepoly (ethylene glycol) (PEG)-b-cholesterol (TATePEG-b-Chol) were fabricated and used as carrier for targeted blood-brain barrier delivery of antibiotics. Ciprofloxacin as a model antibiotic was efficiently loaded into the nanoparticles by a membrane dialysis method. The actual loading level of ciprofloxacin was dependent on initial loading of ciprofloxacin and fabrication temperature. The blank and ciprofloxacin-loaded nanoparticles were characterized using dynamic light scattering and SEM.

    The nanoparticles were spherical in nature, having an average size lower than 200 nm. The uptake of nanoparticles with TAT by human brain endothelial cells was greater than that of the nanoparticles without TAT. Most importantly, the nanoparticles with TAT were able to cross the blood-brain barrier (BBB), and located around the cell nucleus of neurons. These nanoparticles may provide a promising carrier to deliver antibiotics across the BBB for treatment of brain infection.

14. ***Ryuta Saito et al.*** [71]: The investigation determined the impact of key physical and chemical properties of infused molecules on the

extent of CED-mediated delivery. For simple infusates, CED distribution was significantly increased if the infusate was more hydrophilic or had less tissue affinity. Encapsulation of tissue-affinitive molecules by neutral liposomes significantly increased their tissue distribution. The poorer brain distribution observed with cationic liposomes, due to their greater tissue affinity, was completely overcome by PEGylation, which provides steric stabilization and reduced surface charge. Finally, liposomal encapsulation of doxorubicin reduced its tissue affinity and substantially increased its distribution within brain tumor tissue. Taken together, the physical and chemical properties of drugs, small molecules and macromolecular carriers determine the tissue affinity of the infusate and strongly affect the distribution of locally applied agents. Thus, an increased and more predictable tissue distribution can be achieved by reducing the tissue affinity of the infusate using appropriately engineered liposomes or other nanoparticles.

**CONCLUSION:** Although a number of strategies have been developed to deliver drugs into brain for patients with brain tumors and other abnormalities treatment. Despite of these approaches, none of them have proved to be satisfactory in each and every case of CNS disorders. This is because the physiology of the brain presents unique challenges, including tight regulation of what can enter the brain space and limited distribution of substances along ECF flow pathways. A wide range of investigations have been made in the area of brain transporter chemistry and other mediators leading to solving the difficulty in delivery of peptides into brain effectively. But despite of this, the area of transporter chemistry is still a cumbersome and requires potential interest by researchers. Transnasal route of drug delivery give the impression to be superior strategy for achieving enhanced bioavailability in brain. It not only bypasses the BBB and hepatic first pass metabolism (when orally administered) but is also a shortest pathway for rapid drug absorption and quick onset of action. This route also, needs more attention of researchers for safe trafficking of neurotherapeutics to the brain.

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