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BLOOD-BRAIN BARRIER – ITS IMPLICATION IN DRUG TRANSPORT: NOVEL STRATEGIES IN DRUG DELIVERY TO THE BRAIN

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Review Article
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ABSTRACT

The brain is a fragile organ as well as complicated. The brain is protected from many toxic substances and various chemicals by the presence of two barriers namely blood brain barrier (BBB) and blood cerebrospinal fluid barrier (BCSFB). BBB it protects the brain because of restrictive angio - architecture with endothelial cells, tight junctions and peculiar transport system. The routes of drug targeting to the brain now become an important tool in the pharmaceutical field because of many complicated diseases of the brain. There are some limitations for the trans nasal drug delivery, trans cranial drug, BBB disruption, lipidization of molecules for delivery of drugs., Therefore various novel technologies are entered like nanotechnology, liposomal drug delivery and Molecular Trojan Horses. This review includes endogenous transporters which place a role in transport of drug in to the brain, drug delivery in to the brain along with limitations and discussed the novel routes of drug delivery in to the brain.

KEYWORDS: Blood brain barrier, Drug delivery, Transporters, Nanotechnology,

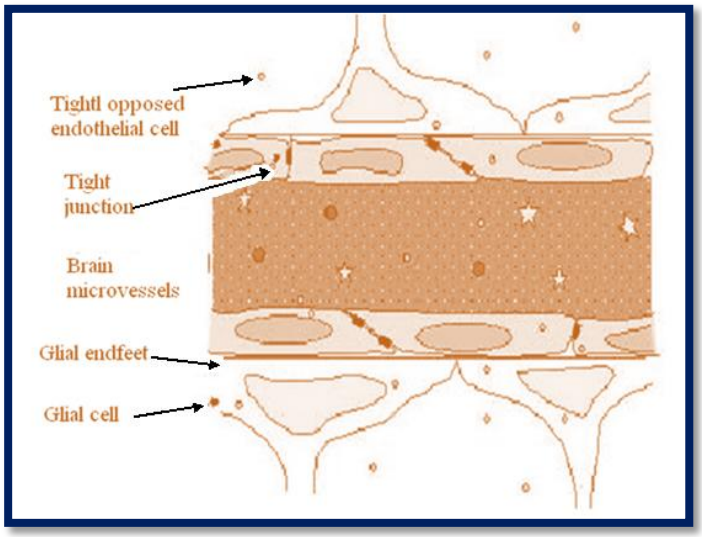
Introduction

Treating central nervous system diseases like alzheimer disease, stroke/neuroprotection, brain and spinal cord injury, brain cancer, HIV infection of the brain, various ataxia producing disorders, amytrophic lateral sclerosis (ALS), Huntington disease, and childhood inborn genetic errors affecting the brain is very challenging because of the presence of a variety of formidable obstacles that obstruct drug delivery. Physiological barriers like the blood-brain barrier and blood-cerebrospinal fluid barrier as well as various efflux transporter proteins make the entry of drugs into the central nervous system very difficult [1].The concept of blood brain barrier (BBB) was introduced by Paul Ehrlich. The blood–brain barrier is specialized system of blood capillary endothelial cell (BCEC) that protects brain from harmful substances in the blood, while supplying the brain with the required nutrient for proper function. The barrier also plays an important role in the homeostatic regulation of the brain microenvironment necessary for the stable and co-ordinated activity of neurons [2]. There are additional types of barriers in the brain except blood brain barrier. Some of these are Blood cerebral spinal fluid barrier, Blood dorsal root ganglia barrier. The BBB present in all brain regions except for the circumventicular organs including area postrema, median eminence, neurohypophysis, pineal gland, subfornical organ, and lamina terminalis [3].

The BBB is formed by brain capillary endothelial cells (BCEC), which are surrounded and Supported by astrocyte foot processes and pericytes. The circumference of the capillary lumen is enclosed by a single endothelial cell. The endothelial cells of the BBB are Distinguished from those in the periphery by increased mitochondrial content [4], a lack of fenestrations [5], minimal Pinocytotic activity [6], and the presence of tight junctions (TJ), which limit Para cellular transport [7].

Inter endothelial junctional complexes in brain blood micro vessels are believed to be one of the main factors responsible for the tightness of the BBB. TJs are depicted as a set of continuous intra membranous strands or fibrils that impose a passive, non selective obstruction to solute exchange between blood and brain interstitial fluid and for the maintenance of cell polarity [8].The anatomy of blood brain barrier shown in **Figure 1.**

Figure 1: Anatomy of the blood-brain barrier



Essentially 100% of large molecules including peptides, recombinant proteins, monoclonal antibodies, RNA interference-based drugs and gene therapies, do not cross the BBB. A misconception is that small molecules readily cross the BBB. However, in fact, greater than 98% of small-molecule drugs do not cross the BBB, except some natural peptides and proteins such as insulin [9].

Endogenous BBB transporters:

Movement of drug across the capillary endothelial barrier is a process of movement through two membranes in series, the luminal membrane and the albuminal membranes of the capillary endothelial cell. Two membranes are transported by endothelial cytoplasm. These two membranes are separated by only 200nm of endothelial cytoplasm. The endogenous transporters are expressed on the luminal and albuminal membranes of the brain capillary endothelial cell [10]. The location of the transporters mentioned in **Figure 2**.

The endogenous BBB transporters can be classified into three categories:

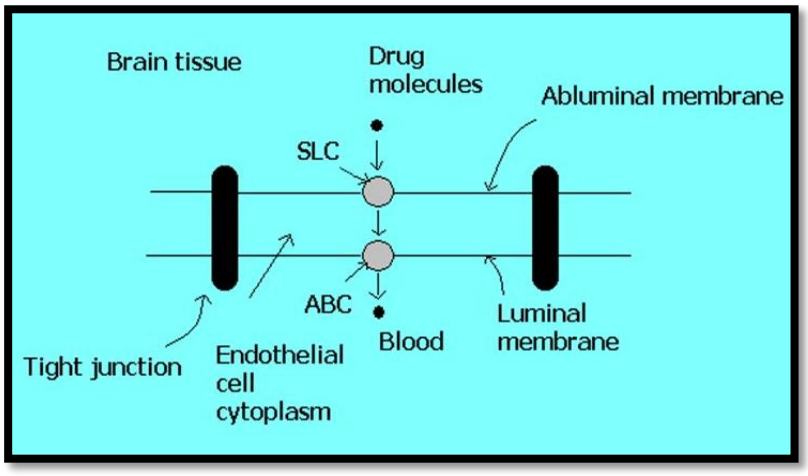
Carrier Mediated Transporters (CMT), Active Efflux Transporters (AET), and Receptor Mediated Transporters (RMT**).** CMT and AET Systems are responsible for the transport of small molecules between blood and brain, the RMT systems are responsible for the transport across the BBB certain endogenous large molecules. Examples of these systems are

listed in **Table 1**. The CMT systems usually mediate brain to blood influx of substrate, although the CMT systems can also mediate brain to blood efflux. The AET systems usually mediate brain to blood efflux of substrate [11, 12].

Table 1: Blood brain barrier endogenous transporters

Carrier-mediated transporters (CMT)	Active efflux transporters (AET)	receptor-mediated transporters (RMT)
Glucose transporter (GLUT1)	Adenosine triphposphate binding cassette(ABC or P-gp)	Insulin receptor (INSR)
Large neutral amino acid transporter(LAT1)	ABC transporter, subfamily C (ABCC)	Transferrin receptor (TFR)
Cationic amino acid transporter (CAT1)	ABC transporter, subfamily G (ABCG2)	Insulin-like growth factor receptor (IGF1R)
Mono carboxylic acid transporter (MCT1)	Organic anion transporter (OAT or SLC22)	Insulin-like growth factor receptor (IGF2R)
Concentrative nucleoside transporter (CNT2)	Organic anion-transporting polypeptide (OATP or SLC21)	Leptin receptor (LEPR)
Choline transporter (CHT)	Glutamic acid amino acid transporter (EAAT or SLC1)	Fc fragment of IgG receptor transporter (FCGRT)
Nucleobase transporter (NBT)	Taurine transporter (TAUT or SLC6)	Scavenger receptor, class B (SCARB1)

Figure 2: Location of transporters in BBB.



Carrier-mediated transport:

Endogenous substances and nutrients are actively transported by highly selective

membrane bound-carrier systems. The expression of these carriers is often polarized to optimize substrate transport into the brain. Several carrier systems have been described in brain capillaries including those specific for small-molecule peptides, hexoses, monocarboxilic acids, amino acids, organic anions and cations, neurotransmitters and nucleosides. Although the exact mechanisms of carrier-mediated influx of many substrates are unknown, this process probably involves the formation of transient narrow pores induced by binding of the respective substrate to the carrier, which then allows only the passage of the specific substrate molecule. Utilization of these carrier systems expressed at the BBB might be an attractive strategy for therapeutic delivery of other peptides and proteins drugs that would otherwise have minimal access to the CNS [13, 14].

Active efflux transport:

The most studied efflux transport system at the BBB is P-glycoprotein, which is a product of the ABCB1 gene (**Table 1**). There are multiple other members of the ABC gene family that represent energy dependent active efflux transporters at the BBB, including members of the ABCC and the ABCG2 gene family. In addition, active efflux transport of drug from brain to blood is a process mediated by two transporters in series, including an energy-dependent transporter and an energy-independent transporter. The energy dependent transporter from ABC gene family can be expressed at the luminal membrane, whereas the energy-independent transporter can be expressed at the albuminal membrane of the brain capillary endothelial cell. The energy-independent transporters are members of the solute carrier (SLC) gene families and include members of the OAT organic anion transporters, acidic amino acid transporters such as the members of the EAAT family or active efflux transporters such as the TAUT taurine transporter (**Table 1**). It is also possible that the energy-dependent transporter is present at the albuminal membrane, whereas the energy-independent transporter present at the luminal membrane [13].

P-glycoprotein:

The first identified and best studied ABC transporter is the multi drug resistance (MDR1) gene product P-glycoprotein (P-gp, ABCB1). P-gp is a 170-kDa phosphorylated glycoprotein, which acts as a multispecific, ATP-driven drug efflux pump [15]. Over expression of P-gp in tumor cells causes multidrug resistance in these cells [16]. P-gp is expressed in endothelial cells of the blood-brain barrier predominantly on apical membrane [17]. The MDR1 gene is encoded by two genes (mdr1a, mdr1b) with overlapping substrate specificity. While mdr1a is expressed in brain capillaries mdr1b is only found in brain parenchyma[18]. P-gp has a broad substrate specificity including organic cations, weak organic bases, some organic anions and some uncharged compounds, such as polypeptides and polypeptide derivatives. Thus it appears that P-gp can handle various classes of drugs including chemotherapeutics, immunosuppressant, antibiotics, anti-HIV drugs,opioids, and calcium channel blockers[19].

Studies using mdr1a/b gene knockout mice, show that P-gp deficient mice exhibit significantly elevated drug levels, particularly in the brain [20, 21]. On the other hand, there is a loss of protection and subsequent neurotoxicity by the loss of P-gp function, which has been observed during the treatment of mdr1a gene knockout mice with the antihelminthic ivermectin. The enhanced uptake compared to ivermectin-treated control (wild type) mice, leads to significantly elevated drug concentrations in the brain, resulting in dramatic neurotoxicity[22]. rifampicin (rifampin) within the lining cells of

the gut causes digoxin to be ejected into the gut more vigorously. This results in a fall in the plasma levels of digoxin. In contrast, verapamil appears to inhibit the activity of P-glycoprotein, and is well known to increase digoxin levels. Ketoconazole also has P-glycoprotein inhibitory effects, and has been shown to increase CSF levels of ritonavir, possibly by preventing the efflux of ritonavir from the CNS. Thus the induction or inhibition of P-glycoprotein can have an impact on the pharmacokinetics of some drugs. Many drugs that are substrates for CYP3A4 are also substrates for P-glycoprotein. Digoxin and talinolol are examples of the few drugs that are substrates for P-glycoprotein but not CYP3A4. By using the P-gp inhibitors ex: verapamil, valspodar we can inhibit the efflux of drugs like anticancer drugs that are substrates of P-gp and restores drug sensitivity in multidrug resistant cell leukemia lines [23].

Multidrug resistance-associated proteins (MRPs, ABCC family) belong to the ABC superfamily of membrane transporters. Until now, 13 members of this family (including MRP1-9) have been identified [24]. However, compared to P-gp, the data on these ABC transporters in the BBB is much more limited **24**. MRPs transport organic anions (e.g. methotrexate), glutathione, glucuronide-conjugated compounds, various nucleoside analogs, but also neutral drugs. Therefore P-gp and MRPs have overlapping substrate specificity, so that several drugs are substrates for both families [25].

Breast cancer resistance protein (BCRP) ABCG2 (MCF-7/AdrVp) Doxorubicin-resistant breast cancer Like all members of the ABCG subfamily, it is a ABC half transporter that forms a functional homodimer The substrate specificity of BCRP is broad, comprising a wide variety of drugs (e.g. mitoxantrone, topotecan, and prazosine), carcinogens and dietary toxins Besides the BBB, BCRP is expressed in placenta, bile canaliculi, colon, and small intestine. BCRP has several substrates in common with P-gp, such as doxorubicine, daunorubicine, and rhodamine-123 [26,27].

Pantoprazole only has a minimal effect on CYP3A4 and has been safely used in patients with peptic ulcers so far, which is a promising prerequisite for its safe use in patients. A potential application may be the combined use with anticancer agents, which could lead to an enhanced CNS penetration of these drugs [28].

Receptor-mediated transport:

Certain large-molecule peptides in the blood undergo RMT across the BBB via the endogenous peptide receptors .The transport of peptides and proteins across cellular barriers has been documented in a number of systems like insulin, insulin like growth factores IGF1 IGF2, angiotensin II ,atrial and brain natriuretic peptide (ANP, BNP), IL-1 and transferrin .However receptor mediated endocytosis across the BBB in vivo has been shown for few peptides and proteins like insulin, transferrin, certain cytokines and leptin while angiotensin II and ANP may exert their effects by binding on the luminal cytoplasmic membrane of brain microvessel endothelia, and may even be involved in the regulation of BBB permeability for other substances [9-13].

Mechanism of receptor-mediated transport:

First is the binding of the ligand to its specific membrane receptor localized at the luminal membrane of brain, this receptor–ligand binding then induces an endocytic event in the luminal membrane that probably involves aggregation of receptor–ligand complexes within pits. The pits further trigger the formation of endocytic vesicles of about 100 nm diameters (endocytosis). These endocytic vesicles can then enter a pathway, which carries them across the endothelial cell, where dissociation of the ligand from the receptor

occurs. Afterwards, the free receptor is recycled to the cell surface. Then ligand-containing vesicles can be packed into export vesicles directed to exocytosis on the abluminal face of the endothelial cell, resulting in transport of peptides/proteins across the BBB [14].

Drug delivery in to the brain:

These delivery systems include transcranial brain drug delivery, trans-nasal brain drug delivery, BBB disruption and small molecule lipidization. But these delivery systems have some limitations for existing brain drug delivery strategies.

Trans-cranial drug delivery to the brain:

Drugs can be delivered to the brain by first drilling a hole in the head, and this encompasses three basic delivery methods: intracerebroventricular (ICV) injection, intra-cerebral (IC) implantation and convection-enhanced diffusion (CED). The ICV administration of glial-derived neurotrophic factor (GDNF) was recently attempted for the treatment of Parkinson's disease [29]. There was no therapeutic effect in patients because the neurotrophic factor did not reach the striatum of brain, and there were a significant number of adverse events related to the trans-cranial delivery system[30]. An advantage of this route is that a wide range of compound and formulation can be considere€d for ICV or IC administration. Thus, both large and small-molecule can be delivered, either alone or in various polymer formulation, to achieve sustained release. Hoistad et al reported a diffusion distance of only 1mm following striatal IC infusion of radio labelld dopamine and mannitol in rats [31, 32].

Trans nasal drug delivery to the brain:

In nasal drug delivery the drug first passes to the respiratory epithelial, from this drug is absorbed into the systemic circulation by Tran cellular and Para cellular passive absorption, carrier mediated transport, or absorption through transcytosis [33].The nasal instillation of lipid-soluble small molecules, such as progesterone, results in a CSF concentration of drug that exceeds the plasma concentration [34].this indicates a direct movement of the drug from the sub mucus space of the nose into the CSF compartment of brain. In recent studies, intranasal administration of wheat germ agglutinin horseradish peroxidase resulted in a mean olfactory bulb concentration in the nanomolar range. In recent studies, intranasal administration of wheat germ agglutinin horseradish peroxidase resulted in a mean olfactory bulb concentration in the nanomolar range. In theory, this strategy could be effective in the delivery of therapeutic proteins such as brain-delivered neurotropic factor (BDNF) to the olfactory bulb as a treatment for Alzheimer's disease [35]. Most pharmaceuticals are water soluble are have MWs >400 Da, and do not freely traverse biological barriers. So local injury has been induced with the trans-nasal delivery system, thus leading to a breakdown of the nasal mucosal barrier [36].

BBB disruption:

The BBB can be transiently disrupted by a variety of means such as intra-carotid arterial infusion of hyperosmotic solutions, noxious agents including vasoactive compounds or local ultrasonic irradiation of the brain. Examples are dimethyl sulfoxide, ethanol, metals, glycerol and polysorbate-80 X-irradiation[37]. The example of this is the injection of mannitol solution to the arteries in the neck. The resulting high sugar concentration in brain capillaries takes up water out of the endothelial cells, shrinking them thus opening tight junction. The effect lasts for 20-30 minute, during which time drugs diffuse freely, that would not normally

cross the BBB. This method permitted the delivery of chemotherapeutic agents in patients with cerebral lymphoma; malignantglioma and disseminated CNS germ cell tumours [38]. The problem with BBB disruption is that this approach to brain drug delivery allows for the leakage of plasma proteins into the brain. Albumin is toxic to astrocytes, and astrogliosis is induced when brain comes in contact with blood [39, 40].

Lipidization of small molecules:

The water-soluble drugs convert in to lipid-soluble so that it can cross the BBB. There are two ways that a drug can be lipidated. First, the polar functional groups on the water soluble drug can be masked by conjugating them with lipid-soluble moieties. Second, the water-soluble drug can be conjugated to a lipid-soluble drug carrier. For BBB transport, the upper limit in molecular area appears to be about 80 Å2, which corresponds to a Mr of less than 300– 400 Da. If the size of the drug is doubled from 50 Å2 (Mr about 250-Da) to 100 Å2 (Mr about 400-Da), the BBB permeation decreases by 100-fold.6 Thus, if the lipidation of a drug causes a significant increase in square area of the molecule, the drug may be too large to effectively cross the BBB. The fact that membrane permeation does not increase in proportion to the increase in lipid solubility [41]. Acetylation of morphine to form heroin. Morphine has two hydroxyl groups and acetylation of both hydroxyl groups results in the formation of heroin. The removal of each hydroxyl group results in the removal of two hydrogen bonds formed between the drug and solvent water. There is an another rule , the BBB permeability of a drug decreases 1 log order in magnitude for each pair of H-bonds added to the molecule in the form of polar functional groups. Based on H-bonding rules the number of H-bonds that a given drug forms with water can be calculated by inspection of the chemical structure, If the MW of the drug is >400 Da and/or the drug forms eight or more H-bonds, then the drug is probably a poor CNS-penetrating molecule [13, 31].

Limitations of these drug delivery systems:

Injury to the brain or nasal mucosa leads significant number of adverse effects. Currently, CNS drugs that are capable of crossing the BBB are mostly small molecule drugs that cross via passive diffusion. But transporters particularly P- gp actively push the molecule out of the Brain. Small molecule compounds do not carry significant concentration of drugs, making it necessary to overload a patient with the compound in order to transport the necessary dosage. The process of these drug delivery is Costly & risky.

Present-day CNS drug-development programs are facing severe challenges in the discovery and development of new drugs for the many disorders of the brain. These challenges derive from (i) the extent to which the BBB limits brain uptake of virtually all drug candidates [41] and (ii) the limitations of the traditional or chemistry-based approaches to solving the BBB problem. We have to consider the biology-based approaches to the BBB problem.

Novel strategies in drug delivery in to the brain:

Due to the drawbacks of small-molecule drugs that cross the BBB via passive diffusion, researchers are concentrating on permeation of the brain by drugs that are actively transported across the BBB.

Nutrient Transporter:

Using endogenous nutrient transporters that are members of the solute carrier (SLC) transporter family, small molecules can cross the BBB in a process known as carrier-mediated transport (CMT). CMT transports

nutrients such as glucose, other sugars, lactate, nucleosides, fatty acids, and vitamins, as well as some hormones into the brain. SLC transporters can be found in the brain and also in the intestinal endothelium, where nutrients (and drugs) are transported from the intestine into the bloodstream. By modifying the chemical structure of a drug to resemble that of nutrients, researchers are able to design drugs that use CMT to cross the BBB by specific SLCs [42, 43]. L-DOPA is a drug that uses such a technique, because dopamine cannot cross the BBB, it must be introduced as L-DOPA, an amino acid that can be taken up by the amino acid transporter. After L-DOPA is transported to the brain, it is converted to dopamine. L-DOPA is therefore a "prodrug" that is able to cross the BBB and be converted into its active form once inside the brain [31, 44].

Receptor-Mediated Transport:

Receptor-mediated transport (RMT) is used by the brain to transport proteins, peptides, and lipoproteins necessary for brain function across the BBB. A ligand is a substance that is able to bind to and form a complex with a molecule to serve a biological purpose. Through a process known as receptor-mediated transcytosis, a ligand is able to cross over from inside of an endothelial cell, through the cell membrane, and into the brain. This is yet another path that researchers have been able to take advantage of in order to breach the BBB. p97. Melanotransferrin, is a cell surface antigen and a member of a group of closely related iron-binding proteins. p97 is the only molecule in the transferrin family that is directly associated with the cell membrane. Cells obtain iron and transferrin by binding to the cell-surface-oriented transferrin receptor (TR), which binds to iron-loaded transferrin and internalizes the complex by the mechanism of receptor mediated endocytosis (RME) [31] P-97 has demonstrated a unique potential as a new plat form to carry therapeutic drugs across the BBB. It's a novel approach to drug therapy. (Biomarker-targeted drug delivery system) In treatment of many of diseases like Alzheimer's disease, brain tumours [45].

Limitations: Hypersensitivity resulting in hyper immunity against foreign monoclonal antibody carrier limits after repeated treatments [43]. Potential toxicity when many targeted receptors are widely expressed in tissues other than the brain [46]. Saturation of the receptor with an antibody [47, 48, 49]. Low dissociation rate of the antibody and recycling of the receptor back to the blood. Finally, and most importantly, none of the novel transporters, carriers, or delivery systems have proven effective in treating diseases of the CNS that require crossing the BBB [46].

Nanoparticle drug delivery system:

Nanopartiacles are sub-micron-sized colloidal structures composed polymeric particles made of natural or artificial polymers ranging in size between about 1 and 1000 nm (1 mm) [50].which is made up of poly (alkylcyanoacrylates) (pacas), polyacetates, polysaccharides, and copolymers. The methods of preparation of nanoparticles .The first drug that was de-livered to the brain by this system hexapeptidedalargin, aLeu-enkephalin analogue [51]. Nano particles shown in **Figure 3**. This system have still greater potential for many applications, including anti-tumors therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines and as vesicles to pass the BBB [52, 53]. Intravenously injected doxorubicin-loaded polysorbate 80-coated nanoparticles lead to 40% cure in rats with intra cranially transplanted glioblastomas. Valproic acid-loaded nanoparticles showed reduced toxic side effects of valporate therapy [54].

Advantages of nanotechnology:

1) Due to their small size nanoparticles penetrate into even small capillaries and are taken up within cells, allowing an efficient drug accumulation at the targeted sites in the body.

2) The use of biodegradable materials for nanoparticle preparation, allows sustained drug release at the targeted site after injection over a period of days or even weeks.

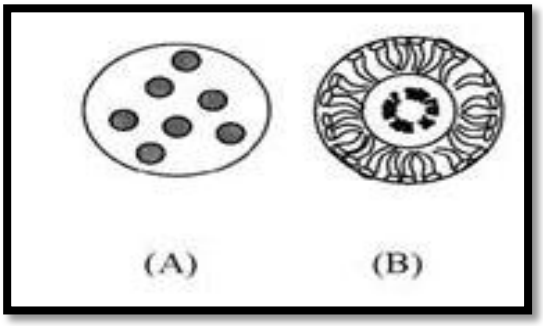
3) To improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers.

Liposome drug delivery Liposomes are lipid vesicles first characterized by Bangham [55].liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer composed of biocompatible and biodegradable lipids similar to biological membranes. Cholesterol, an important constituent of many cell membranes is frequently included in liposome formulations because it reduces the permeability and increases the stability of the phospholipid bilayers. The biophysical properties of liposomes such as size, surface charge, lipid composition and amount of cholesterol are various and able to control distribution, tissue uptake and drug delivery. Liposomes can be prepared with diameters ranging from 20 nm to 100 mm. Liposomes shown in **Figure 3**.

Figure 3: Nano particles and liposomes used in drug delivery

(A) Nanospheres with drug particles distributed throughout a polymer/lipid matrix

(B) Liposomes with Multilamellar vesicles



Recent studies revealed that a new formulation of small sized (less than 100 nm) long circulating liposomes appears to offer selective tumor localization. This localization is probably related to long circulation time of liposome and to increase probability for extravagation to the tumor vascular endothelium. It has also been demonstrated that the selective tumor localization of doxorubicin encapsulated in stealth liposomes (SLs) is associated with superior therapeutic activity over free drug activity in various systemic models [54]. Palliative effects of calpain inhibitor and copper zinc superoxide dismutase (Cu/Zn SOD), when administered as liposome complexes, in controlling ischemia-induced neuronal damage was demonstrated when compared to the corresponding substances in non-encapsulated manner Similarly, when liposomes containing GABA were administered intraperitoneally to rats with penicillin-induced epileptic activity, the formulation decreased or prevented the epileptic activity, in contrast to free GABA.

Another study reported that liposome-entrapped phenytoin suppressed amygdaloid epileptogenic attacks induced by dibutyryl-cAMP/EDTA in rats [56].

BBB Transport of large – molecule drugs with Molecular Trojan Horses:

Trojan horses are genetically engineered proteins that have the capability to cross BBB (mAb).Peptides, recombinant proteins& antisense agents such as peptide nucleic acids conjugate with Molecular Trojan Horses for delivery across BBB following intravenous administration [31] VIP (vaso active polypeptide) is a potent cerebral vasodilator. Does not cross the BBB. The VIP-TFR mAb conjugate can cross BBB on intravenous administration.FGF2 (Fibroblast growth factor) is a potent neuroprotectve agent. i.v administration of FGF2-TFRmAb conjugate decreases brain ischemia. Aβ-TFRmAb conjugation: detection of brain amyloid by brain imaging [13].

CONCLUSION:

The blood–brain barrier can no longer be ignored as a factor greatly limiting the entry of therapeutic drugs in to the CNS. According to Pardridge, over 98% of small molecules and close to 100% of large molecules do not cross the BBB. This is because of restrictive angioarchitecture of the BBB with endothelial cells, tight junctions and peculiar transport system. This makes the biggest obstacle for the treatment of CNS diseases. Few pharmaceutical companies actually have a BBB drug targeting effort. However, concerted effort such as the international BBB consortium will allow the design of better multi- centre trials eventually powered to answer whether or not this approach is worthwhile in the treatment of different CNS pathologies. We are tending to adopt a more open-minded approach toward alternative treatment strategies emphasizing CNS delivery.

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