A Review on Pharmaceuticals Approaches on Drugs Crossing Blood Brain Barrier

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ABSTRACT

The blood brain barrier is a semipermeable and extremely selective system in the central nervous system of most vertebrates that separates blood from the brain extracellular fluid. It plays a vital role in regulating the transport of necessary material for brain function furthermore, protecting it from foreign substance in the blood that could damage it .The blood brain barrier (BBB) is a diffusion barrier, which impeded influx of most compounds from the blood brain. Three cellular elements of the brain microvasculature compose the BBB-endothelial cells, astrocyte end-feet, and pericyte (PCs).The blood-brain barriers playing a critical role in controlling the influx and efflux of biological substances essential for the brain's metabolic activities as well as neuronal function. The blood-brain barrier (BBB) is a highly selective membrane barrier at the brain micro vessel level that facilities transport between the systematic circulation and the central nervous system. A growing body of the evidence supports a major role of BBB in the etiology and the pathogenesisof multiple vascular and neurodegenerative disorder.

Keyword: *Blood-brain barrier, derecerebrospinal fluid, endotheliun, receptors, vascularbiology.*

INTRODUCTION

The capillary boundary that is present between blood and brain is called blood-brain barrier(BBB).

In the brain capillaries, the endothelial cells are joined by tight junction which form blood brain barrier (1). The BBB serves role other than that of blocking circulating substance from entering the CNS. It also facilitates and regulates the entry of many substances that are critical to CNS function and secretes substances into the blood and CNS. These extra-barriers functions allow the BBB to influence the homeostatic, nutritive, and immune environments of the CNS and toregulate the exchange of informational molecules between the CNS and blood (2).
To develop new drug for central nervous system (CNS), the blood brain barrier is the ratelimiting factor for these drugs.

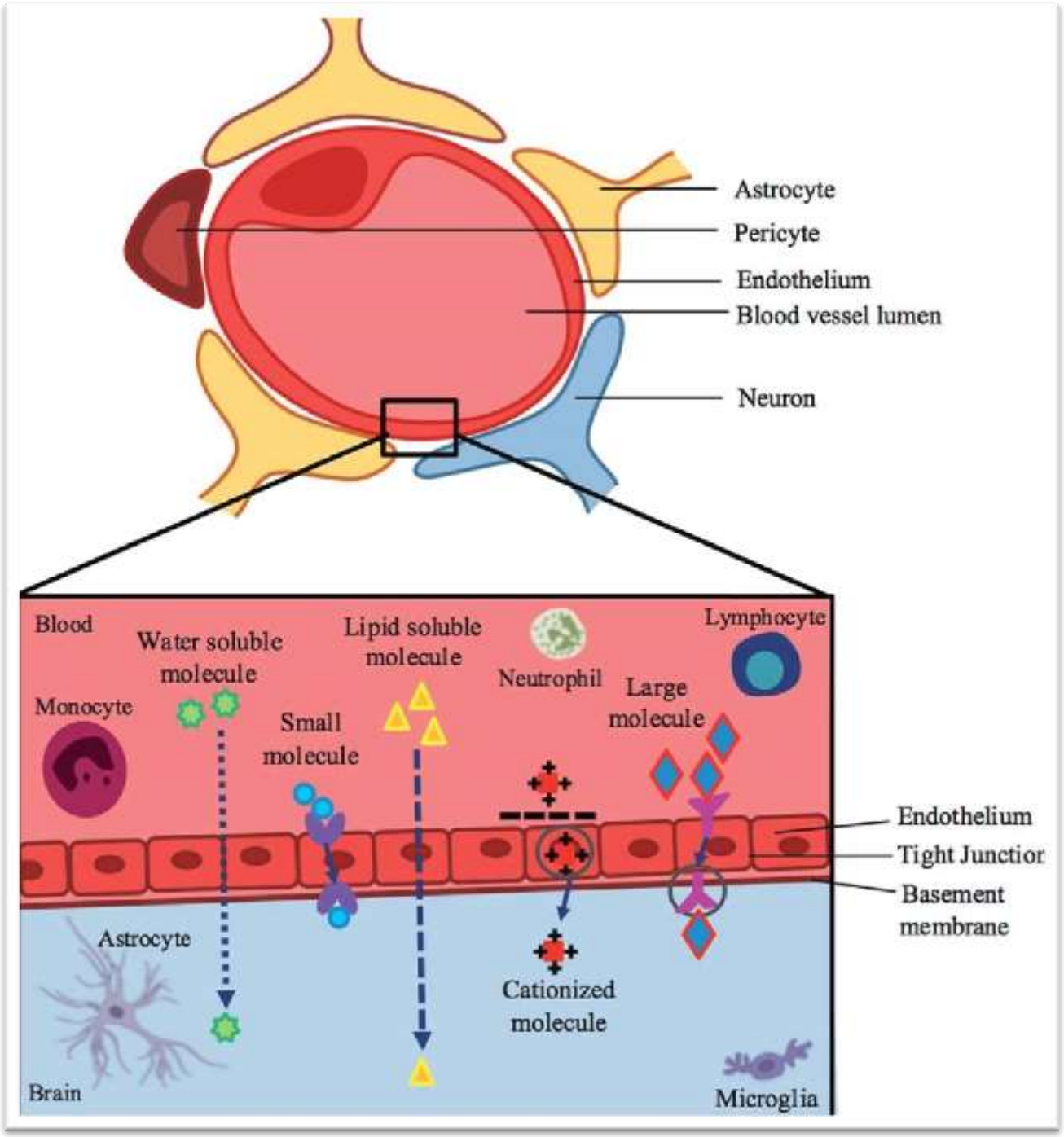

Fig. No. 01: A Schematic representation of blood brain barrier and pathway across this barrier.

Misconception regarding small molecules is, they readily cross the BBB. However, in fact, >98% of all small molecules do not cross the BBB (6). Only small molecules that are lipid soluble and also have a molecular weight < 400 Da can cross the BBB; most macromolecules cannot penetrate brain endothelium. This physiological hurdle of the BBB stops 95% of molecules for drug development. Recently, studies have demonstrated that the BBB is a dynamic interfacecontrolling entry of substances into the brain from the blood (7,8).

Drug development for brain diseases has the poorest success rates compared to othertherapeutic areas.

The time for developing CNS drugs is normally much longer than for non-CNS drug. Clinical trials of CNS drugs become challenging because of the complexity of the brain, side effects and impermeable blood-brain barrier (BBB) (7,9). Drug discoveries continue to be made in plentiful numbers but even through the novel therapeutic molecules give good results in the early phase of drug development; they often fail to successfully clear subsequent clinical trials, owing in part to their inability to cross the BBB. The 2014 statistics of top global therapy areas interms of sales, only two CNS therapy areas, i.e., pain and mental health-related products (10). The permeability of the BBB is mainly controlled by inter endothelial junctions that are protein complexes such as adherents junctions, TJs, and gap junctions (11). The BBB is a complexsystem made up of a structurally distinct, continuous endothelial cell layer separating the blood from the extracellular fluid of the brain. The luminal plasma membrane of the endothelial cells is directed towards the blood, while the abluminal plasma membrane faces the brain (12). The presence of adhesion molecules and junctions between endothelial cells and the low density of pinocytosis æsome of the key structural features that make the BBB selectively permeable (13). Clinical trials of CNS drugs become challenging because of the complexity of the brain, sideeffects and the impermeable blood-brain barrier.

1. TRANS-CRANIAL DELIVERY:

The old way of transfer the drug via trans-dermal delivery system by drilling the hole in the head, and this encompasses three basic delivery methods: intra-cerebral (IC) implantation, intra cerebroventricular (ICV) injection and convection-enhanced diffusion (CED). The ICV administration of glial-derived neurotrophic factor (GDNF) was recently attempted for the
treatment of PD (Parkinson's diseases) (14,15). The factor limiting either the intracerebral or ICV infusion approach is that either method relies on diffusion for drug penetration into the drug brain for depot site. In this no therapeutic effects was shown in patients because theneurotrophic factor did not reach the striatum of brain, and there was significant number of adverse events related to the trans-cranial delivery system. The penetration of neurotrophins such as GDNF into the caudateputamen nucleus of brain parenchyma from the cerebrospinal fluid (CSF) flow tracks is not expected. The rate of CSF exodus is faster than the rate of solute diffusion into brain parenchyma from the ependymal surface. Diffusion in brain is slow as compare to the rapidbulk flow of CSF in brain.

The 140 ml volume of CSF in the human brain is completely turned over every 4-5 hours, and exits the brain to blood. So, ICV drug delivery to brain shows high drugexposure at the ependymal surface of the brain, which can cause sub ependymal astroglioticreaction (16,17).
The new approach or technology is based on knowledge of endogenous BBB transporters, andaims to reformulate drug structures so that these molecules can cross the BBB via endogenoustransport system.

2. ENDOGENOUS TRANSPORTERS / PHYSIOLOGICAL DRUG TRANSPORTERS:

The anatomical basis of the BBB is the brain microvascular endothelial barrier. In human brain there are >100 of billions capillaries present and each neuron is virtually perfused by its ownblood vessels (18). In human brain length of capillary is ~400miles and the surface area of BBB is ~20m.The brain microvasculature comprise four cells which includes the endothelial cell, the pericyte (they shares the basement membrane with the endothelial cells), the astrocyte footprocess (which inverts ~90-98% of brain surface of the microvasculature) and the nerve endings thatend directly on the vascular surface. These four cells contribute the functioning of the microvasculature in brain. The permeability properties of the BBB are controlled only by the capillary endothelial cell. The pericyte, astrocyte and the basement membrane do not constitute any significant permeability barrier to solute across the capillary endothelial barrier is a process movement through two membrane in series, the luminal and albuminal membranes are separated by only 200nm of endothelial cytoplasm (19).The endogenous BBB transporters classified into three categories: carrier-mediated transport (CMT), active efflux transport (AET) and receptor-mediated transport (RMT). Carrier-mediated and active efflux transport systems are responsible for the transport of the small drugmolecules between blood and brain , the receptor mediated transport system are responsible for the transport across BBB of certain endogenous large molecules.

3. CARRIER-MEDIATED TRANSPORT (CMT):

In humans body certain endogenous substances such as glucose, amino acids, vitamins and neuropeptides are transported into the brain by presence of some specific carriers at BBB. Those drugs which acts on specific brain part

are modified chemically so that their structure isresemble with endogenous substance of the body and thereby they are being transported by the specificcarrier via carrier-mediated transport. Solute carriers like SLC2, SLC7, and SLC16 are present on the BBB. Glucose transporters (GLUT) form a part of the SLC subgroups. Out of total glucose transporters located on BBB, GLUT1 is localised on the both luminal and abluminal membranes of the BBB endothelial cells(20).

Antiepileptic prodrugs 7-chloronokynurenic acid and nipecotic acid were developed and they were transported by GLUT1. This approach has limitation of only being able to transport the agents that are structurally similar to the endogenous ligands because they will only be transported byendogenous carriers. Even the size of the drug molecules should be similar to the endogenous ligands as the carriers are present on the cell membrane. To overcome these limitations, designing peptide carriers is being trialed. K15apolipoprotein E (ApoE), a synthetic peptide carrier, was designed and synthesized. This carrier has specific property of altering the permeability of the BBB temporarily. K16ApoE was per-mixed with cetuximab and following this, seven different small molecule chemotherapeutic agents were injected (21).

4. ACTIVE EFFLUX TRANSPORT:

The endothelial cell of the brain have several ATP-driven drug efflux pumps, such as multidrug resistant protein and P-glycoprotein (P-gp), which is responsible for the transport of drug out of the brain to the blood. Many multidrug-resistant proteins efflux out cationic, amphiphilic, aswell as neutral compounds, while P-gp is responsible for the efflux of lipophilic compounds. Thus,inhibition of the efflux pumps can serve as an important approach for brain targeting. GNE-317 and GDC-0980 are two phosphatidylinositol 3-kinase PI3K/mechanistic inhibit efflux pumps. Inhibition of P-gp as a strategy is also explored for the treatment of glioma. Cediranib is a vascular endothelial growth factor receptor inhibitor being investigated for the treatment of awide range of cancers including glioblastoma multiform. BBB active drug efflux transporters of the ATP-binding cassette (ABC) gene family are increasingly recognized as important determinants of drug distribution to, and elimination from, the CNS. The ABC efflux transporter P-glycoprotein (Pgp) has been demonstrated as a key element of the BBB that can actively transport a huge variety of lipophilic drugs out of the brain capillary endothelial cells that formthe BBB. ABC efflux transporters may also limit the central distribution of drugs that are beneficialto treat CNS diseases (22).

5. RECEPTOR-MEDIATED TRANSPORT:

In several diseased conditions, there is up regulation of specific receptors. RMT exploits this property for the active targeting of drugs. A prepared formulation is tagged with a ligand that isspecific to the upregulated receptor, causing it to specifically bind to the receptor. Once ligand receptor binding occurs, receptor-mediated endocytosis takes place. This is followed bymovement of the drug-receptor complex within the endothelial cytoplasm and finally exocytosis of the drug onto the abluminal surface . Certain large-molecule peptides in the blood undergo RMT acrossthe BBB via the endogenous peptide receptors (23).

Insulin in blood undergoes RMT across the BBB viathe endogenous BBB insulin receptor (INSR). The insulin-like growth factors (IGF) IGF-1 and IGF-2 undergo RMT across the BBB. The insulin-like growth factors (IGF) receptor at the human BBB differs from the IGFR at the animal BBB, in that both IGF-1 and IGF-2 bind with high affinity to a single variant IGFR. Several receptors that can be targeted for thedelivery of drugs across the BBB are(24):

5.1 Transferrin Receptors:

Transferrin receptors are the most widely studied receptors for brain delivery transferrin receptors complexes are stable and do not undergo endosomal degradation and thus are easily transported towards the abluminal surface . Studies indicated that thetransport of antibodies was constricted to brain endothelial cells only. Most of the vesicles underwent endosomal degradation and only a few could reach the abluminal membrane.

To overcome this drawback, newer approaches that modified the antibody-binding strengthhave been used so as to mimic endogenous transferrin, so that brain uptake of the antibodies can occur. In such strategy gold nanoparticals with a transferrin ligand was prepared. However, they used acid-cleavable linkage between the transferring and nanoparticle core, which resulted in escapefrom endosomal degradation and increased transport to the parenchymal region. Transferrin receptor-mediated targeting for efficient delivery of small interfering RNA (siRNA) in glioma has also been reported. Layer-by-layer assembling of protamine/chondroitin sulfate/siRNA/cationic liposomes modified at the T7 peptide led to effective penetration of the nanoparticles into the core of the tumor when evaluated using U87 glioma cells and in-vivoimaging studies.

5.2 Folate Receptors:

Folate receptor-mediated endocytosis and brain targeting is another approach with anadvantage of not undergoing endosomal degradation, if prepared skillfully. Micelle-like nanoparticles for delivery of cytochrome c protein using redox-sensitive bonds between nanoparticles and folicacid resulted in efficient brain targeting as depicted in in-vitro and in-vivo brain tumor studies Elongated cellulose nanocrystals decorated with folic acid for targeted delivery of an anticanceragent were developed. The system underwent RMT as shown in cellular binding/uptake studiesin human and rat brain tumor cells.

5.3 Scavenging Receptors:

Scavenging receptors (SRs) are transmembrane glycoproteins serving as targets for modified forms of low-density lipoprotein, i.e., oxidized and acetylated low-density lipoprotein.

Out of several types of SRs, SRA1 and SRB1 are expressed on brain capillary endothelial cells. In-vitro assays confirmed that it undergoes RMT via both Lipoprotein receptor-related proteins RP) receptors as well as class A and B SR. Lipoprotein Receptor-Related Protein Alzheimer's disease is associated with formation of the amyloid precursor protein andalterations

in alpha-2-macroglobulin and apolipoproteins. Lipoprotein receptor-related proteins (LRPs) are signalling receptors serving as receptors for these three peptides. Thus, they play a role in the pathogenesis of Alzheimer's disease. Moreover, these receptors are unregulated in malignant astrocytomas, including glioblastoma cells.

6. TRANSPORT THROUGH COLLOIDAL DRUG-CARRIERS (NANOCARRIERS):

Colloidal drug carriers include nanosized drug-carrier systems, e.g., nanoparticles (polymeric, lipid and inorganic nanoparticles), micelles, dendrimers, nanogels, exosomes and liposomes. These carriers usually are in the nanometer range (1–1000 nm). Colloidal drug-carriers can beused by different physiological mechanisms for drug delivery across the BBB and can be modified to achieve the desired efficacy. Consequentially, several colloidal drug-carriers have been reportedto act as functional nanomedicines in preclinical studies by using animal models for human diseases
Nanoparticles.This approach is mainly based on the use of nanosized technology for drug release in the brain.(25)
This delivery system uses a wide variety of nanoscale drug delivery platforms mainly including lipid- and polymer-based nanoparticles (NPs) that assure a controlled and improved release ofdrug . Considering that NPs have shown to be effective drug carriers, the feasibility of using them for enabling a more effective delivery to organs has been investigated using laronidase surface-functionalized lipid-core nanocapsules.
Polymeric Nanoparticles Polymers from natural as well as synthetic origins are used for the preparation of a polymeric nanoparticulate system. They are classified into two categories, nanospheres andnanocapsules.
Nanospheres, the drug molecules are dispersed throughout or just present on the surface ofthe polymeric matrix.
Nanocapsules, the drug molecules are surrounded by the polymeric shell (reservoir). A widerange of polymers has been investigated for their sustained and targeted drug-release profile. Dual- peptide-functionalized albumin-based nanoparticles with tumor-targeting, cell-penetrating and endolysosomal pH-responsive properties were proposed by Chen et al .Lipid Nanoparticles
Lipid nanoparticles are a drug containing a solid lipophilic matrix with the particle size ranging from 100 to 1000 nm. The term 'lipids' when used in the context of lipid-based nanoparticulate delivery, may be any of the following: waxes, sterols, cholesterol, fat-soluble vitamins, monoglycerides, diglycerides, triglycerides, or phospholipids. The lipid nanoparticles may be considered as derivatives of oil-in-water emulsions, wherein the liquid lipids of oil droplet are replaced by lipids that exist in a solid form at body temperature. The most commonly used nanoparticles, however, fall in the range of 150–300 nm . Most of the lipids used are generallyregarded as safe by the US Food and Drug Administration except Acetyl alcohol.
Inorganic Nanoparticles Nano formulations from inorganic materials, such as metal/metal oxides and silica, are used mainly for imaging/diagnostic purposes. The surface of these nanoparticles can be functionalized to enhance penetration through the BBB. Transferrin-appended, doxorubicin and paclitaxel- loaded, magnetic silica PLGA nanoparticles were developed for the treatment of brain glioma.Micelles are a spherical colloidal system consisting of a hydrophobic core and a hydrophilic surface. They are composed of amphiphilic block copolymers, which tend to aggregate inaqueous solutions to form micelles.
Dendrimers: Dendrimers are enormously branched, three-dimensional, well-organized nanoscopic macromolecules (typically 5000–500,000 g/mol). The three-dimensional structure of dendrimers imparts them with a variety of distinctive properties, such as the presence of well-defined functional groups at the periphery, a globular nanoscaled shape, hydrophilic or hydrophobic cavities in the interior, and a low polydispersity index, and thus a wide range of

potential applications. The word 'dendrimer' arises from the Greek 'dendron', meaning 'tree' or 'branch', and meros meaning 'part'.m'Arboroles' or 'cascade polymers' are the other names for dendrimers.
The efficiency of a dendrimer-based formulation for a poorly water-soluble antipsychotic agent, haloperidol, in targeting the brain via intranasal and intraperitoneal administration routes. The
developed dendrimer system displayed a considerably higher distribution of drug in both plasma and brain as compared with the control formulation delivered by intraperitoneal injection. In addition, the drug-loaded dendrimer formulation, when administered by the intranasal route, produced a behavioral response similar to that of the intraperitoneal injection, but at a 6.7times lower dose.

Nanogels: Nanogels, a class of carrier systems for the delivery of drugs and biomacromolecules, have beenproposed for crossing the BBB. A carboxyl-functionalized poly (N-vinyl pyrrolidone) nanogel system was produced by ionizing radiation as a substrate for the covalent attachment of insulin.

A nanogel system for insulin delivery to the brain has been developed, taking into considerationthe protective role of insulin in Alzheimer's disease. The results of the study revealed that thenanogel system was a suitable vehicle for the delivery of insulin across the BBB and a very promising tool for the treatment of neurodegenerative diseases.

Exosomes: Exosomes are lipid vesicles secreted intracellularly by inward folding of the multi-vesicular body of the membrane and, thereafter, they ooze out of the plasma membrane of the cell. The components of exosomes isolated from brain ECs function as regulators for exchanging molecules across the BBB and maintaining cell-cell communication in the brain. Exosomes have been utilized to deliver small molecules, proteins and nucleic acids to cross the BBB. A detailed review can be found. As they are components from the cell membrane, a circular bubble shape, and nanosized, they have the characteristics for ease of migration from one cell to another andrelease their content like microRNAs and proteins. These exosomes are secreted by all the differenttypes of cells and hence they are found in ample numbers in body fluids such as saliva, blood, andurine.

Liposomes: Liposomes are vesicular drug-delivery systems consisting of an aqueous inner core enclosed by uni-/multi-lamellar phospholipid bilayers. Liposomes can accommodate both hydrophobic and hydrophilic drugs in their phospholipid bilayers and aqueous core, respectively, thus making it a drug-delivery system of choice for systemic delivery of various therapeutics. The phospholipid bilayers consist of naturally produced phosphatidylcholine, sphingomyelin, or glycerophospholipids.

Nanoemulsios: Nanoemulsions are thermodynamically stable, heterogeneously nanosized dispersionsof water in-oil or oil-in-water preparations stabilized by means of an emulsifying agent, i.e., a surfactant and co-surfactant. A risperidone-loaded nanoemulsion was developed for brain-targeted drug delivery The optimized risperidone-loaded nanoemulsions contain sodium oleate in the aqueous phase and polysorbate 80,poloxamer 188, or solutol HS15 as a co-emulsifier with a mean size of 160 nm, size distribution of <0.15, and zeta potential around -50mV. The nanoemulsion was produced by hothomogenization and their ability to improve risperidone delivery to the brain(26).

A saquinavirloaded oil-in-water nanoemulsion system was proposed for achieving brain targeting. Saquinavir in aflax-seed oil nanoemulsion showed maximum plasma concentration and area under the plasma concentration-time curve values five and threefold higher in the brain, respectively, as compared with an aqueous suspension, revealing an enhanced rate and extent of aqueous suspensionabsorption following oral administration of nanoemulsions.

7. TRANS-NASAL DELIVERY:

Nasal delivery is an alternative method to overcome the BBB. The nasal cavity provides access to the brain parenchyma without interference of the BBB. The drugs are delivered to the brain via paracellular, transcellular, and neuronal transport from the neuroepithelium of the nasal cavity to the CNS. The nasal instillation of lipid-soluble small molecules, such as progesterone, results in a CSF concentration of drug that exceeds the plasma concentration, which indicates a direct movement of the drug from the submucus space of the nose into the CSF compartment of brain. However, not all drugs are suitable for nasal drug delivery, since specific physicochemical properties and formulations determine the bioavailability of the drug in the brain. Diffusionacross the nasal mucosal barrier, the drug can cross the arachnoid membrane and enter into olfactory CSF. Once there, the drug will move along the usual CSF flow tracks.

Therefore, delivery of drug to the brain via the nose is very similar to an ICV injection. Generally, lipophilic drugs with low molecular weight show a more ready bioavailability after nasal administration than charged hydrophilic drug. Drug formulations can be modified to increasedrug bioavailability with, for example, liposomes, cyclodextrans, and nanoparticles. In addition, the advantage of drug delivery through the nose is that the drugs are not metabolized by first-pass

metabolism. However, a disadvantage is the small volume that can be administered via intranasal delivery. However, most CNS drug candidates are not the lipid-soluble small molecules that freely cross membrane barriers, including the nasal mucosa. Most pharmaceuticals are water soluble orhave MWs >400 Da, and do not freely traverse biological barriers. Certain drugs that would not beexpected to cross the nasal mucosa have been found to enter into olfactory CSF following intranasal instillation. For drugs other than lipid-soluble small molecules, local injury to the nasal barriers could be a prerequisite for drug transport between the nasal and olfactory CSF compartments (27). One would predict that when drug is administered via trans-nasal delivery in a volume that does not cause local injury, the drug will not distribute to the CSF, and this is what has been experimentally observed for small molecules such as melatonin or vitamin B12 .

Recently, liposomes loaded with a novel β-sheet breaker peptide (H102) were developed for the treatment of Alzheimer's disease. The results of the study revealed a consistent penetrationof the liposomes into the Calu-3 cell monolayers. When administered intranasally, the system delivered the drug load effectively to the brain tissues.

The area under the plasma concentration time curve of H102-loaded liposomes in the hippocampus was reported to be 2.92- fold higher than that of the solution group. It also inhibited further plaque deposition and increased the activities of choline acetyl transferase and insulin degrading enzyme, revealing the potential of the systems for the treatment of Alzheimer's disease.(28).

8. ULTRASOUND & MICROBUBBLES

Focused ultrasound (FUS) in combination with the administration of microbubbles (MBs) is an emerging technique being investigated to enhance the permeation of therapeutics across theBBB in a noninvasive, localized, and transient manner. Microbubble-mediated focused ultrasound (FUS), or sonoporation, is a minimally/non-invasive method for targeted drug delivery into the brain tumor. Upon acoustic pressure from a transducer, microbubbles are pressed against the endothelial cell wall and start to vibrate. The vibration induces stress on the endothelial cellwall resulting in the temporary and local disruption of the BBB. The combination of ultrasound with microbubbles is considered to be safe, since no neuronal damage, apoptosis, ischemia, or long- term vascular damage has been observed upon treatment. The therapeutic window of microbubble-mediated FUS is dependent on the closure dynamics of the BBB after disruption.The BBB slowly closes within several hours, whereas larger molecules such as nanoparticles have a shorter therapeutic window compared with smaller molecule. Drug half life and penetration depth after sonoporation is drug dependent. The heterogeneous nature of theBBB phenotype poses less of a problem for FUS since the focused ultrasound can be applied overthe entire tumor area. Brain tumors with a low vessel density might be less suited for focused ultrasound. The vasculature is important for the delivery of microbubbles and drugs since theblood vessels are key to deliver microbubbles and drugs to the tumor.

Combining FUS with immunotherapy might be a powerful combination for the treatment ofbrain cancer. Immune cells are not able to cross the BBB since CNS endothelial cells have a low expression of leukocyte adhesion molecules . Immune cells can extravagate after the BBB is disrupted with FUS. In vivo studies are now investigating the possibilities of immunotherapy in combination with FUS. The non-invasive nature of FUS in combination with numerous drugs makes FUS a versatile and promising technique for drug and/or immune therapy delivery for various brain tumors.(29).

9. TRANSPORT OF LARGE-MOLECULE WITH MOLECULAR TROJAN HORSES:

Certain peptidomimetic mAbs undergo RMT across the BBB in vivo. The receptor-specific mAb binds to an exofacial epitope on the endogenous BBB peptide receptor, at a site that is spatiallyremoved from the endogenous ligand binding site, and 'piggy-backs' across the BBB on the endogenous peptide RMT system.The most potent BBB molecular Trojan horse known to date is a mAb for the human insulin receptor (HIR), which is active in humans. The molecular Trojan horse carries the large molecule pharmaceutical across the BBB in vivo, to cause in vivo CNS pharmacological actions. This has been reduced to pharmacologic practice in vivo for multipledrug sand experimental model systems. Antisense delivery to brain Certain antisense radiopharmaceuticals such as peptide nucleic acids (PNAs), which hybridize to a specific nucleobase sequence of a target mRNA molecule, could be used as radiopharmaceuticals to image gene expression in-vivo in the brain, providing the antisense radiopharmaceutical is able to cross the BBB. The intravenous administration of PNA alone does not result in imaging geneexpression in brain because the PNA does not cross the BBB.

Non-viral plasmid DNA therapeutics Molecular Trojan horses can deliver non-viral plasmid DNA to brain following intravenous administration with the use of Trojan horse liposomes (THL). The plasmid DNA is encapsulated in a

100 nm pegylated liposome. The tips of 1–2% of the polyethylene glycol (PEG) strands are conjugated with a BBB molecular Trojan horse such as the TFRmAb or the HIRmAb. A 90– 100% increase in survival time was observed in mice with intracranial human brain cancer following the weekly intravenous administration of a plasmid DNA encoding either a 700 nucleotideantisense. RNA against the EGFR or a short hairpin RNA against the human EGFR (30).

10. DISRUPTION OF BBB:

Administration of Vasoactive Substances In-vivo studies in animal models revealed the selective potential of the vasoactive amines [bradykinin (and its analog RMP-7, receptor-mediated permeabilizer) and histamine] in opening of the BBTB. Bradykinin was reported to increase the permeability of the endothelial tight junction by activating the B2 receptor of the endothelial cells. The bradykinin analog, RMP-7, along with transferrin was used to prepare liposomes containing nerve growth factor for the treatment of Alzheimer's disease. The developed formulation was evaluated using a strocyteregulated, human brain micro vascular endothelial cells, which showed increased permeability across the BBB . In addition to bradykinin and histamine, adenosine is another vasoactive substance that has been explored for enhancing BBB permeability. Adenosine acts on adenosine 2A receptors, which belong to the family of G-protein coupled receptors located on the brain capillary endothelialcells.

Osmotic (Chemical or Hypertonic Shock) Disruption Mannitol, the most commonly explored osmotic agent, shrinks the endothelial cells hyperosmotically, thus opening the endothelial tight junction, which further leads to passive diffusion of large molecules across the BBB . Recently, it has been used in combination with nanoparticles, cellular delivery, peptides, and gene delivery Apart from mannitol, there have been other chemical agents explored for the disruption of the BBB; namely, borneol, polydixylitol and lyophosphatic acid . However, apart from its beneficial effects, risk factors are also associated with mannitol therapy such as structural brain damage,expression of heat shock proteins and microembolisms, altered glucose uptake, abnormalneuronal function, and passage of plasma proteins.(31).

11. CONCLUSION:

Progress in the field of pharmaceutics and technology has led to remarkable advancements in brain targeting. Exploiting the inherent mechanisms for the transport of drugs such as adsorptive mediated inhibition of active efflux pumps, receptor mediated transport, and cell-mediated transport has provided promising results. Technological improvements have led to encouraging outcomes using liposomes, nanoparticles, micelles, nanogels, exomers and dendrimers. Alternative routes past the BBB have also shown significant potential for being commercialized like, nasal delivery, trans-carenial delivery etc. Furthermore, to achieve a constructive brain targeted drug-delivery system, some basic concerns need to be addressed in the nearby future,such as factors more emphasis should be focused on the use of biodegradable materials, which get eliminated easily from the brain. A considerable improvement needs to be made in targetingthe efficiency of such systems before their clinical application.

Hydrophobic drugs may leak fromthe delivery system and subsequently enter the brain, thus proof of the enetration of the drug into the brain does not (necessarily) mean penetration of the delivery system itself. Uniform method of preparation should be developed for the development of a nanoparticulate system to achieve amore homogenous and predictable product.

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