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EFFECTIVE NOVEL PHARMACEUTICAL TECHNOLOGIES FOR BRAIN DRUG DELIVERY SYSTEMS: AN REVIEW

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ABSTRACT

The regulated entry of most blood-borne substances into the brain has been recognized for more than a century. The blood-brain barrier shielding function provided by endothelial cells is important in the treatment of neurological diseases because this exclusion of foreign substances also restricts entry of many potentially therapeutic agents into the brain. BBB allows a selective entry of nutrients and minerals across it and limits the entry of foreign substances like drugs as well as neuro pharmaceutical agents. 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 various strategies available and under development for enhancing drug delivery to the CNS are reviewed. The present review enlightens about several novel approaches including nanotechnology based approach like nanoparticles, liposomes, antibody mediated delivery approach and application of genomics in brain drug targeting that would give an insight to the researchers, academia and industrialists.

KEYWORDS: BBB, Nanoparticle, Liposomes, Chimeric peptides, Mannitol.

INTRODUCTION

Disorders of the central nervous system are numerous and affect a large part of the world's population. The neurodegenerative diseases, such as Alzheimer's, Parkinson's diseases and multiple sclerosis are characterized by symptoms related to movement, memory, and

dementia due to the gradual loss of neurons. Stroke, ischemia, human immunodeficiency virus infection, epilepsy, and other psychiatric disorders such as anxiety, depression and schizophrenia conditions that markedly affect the morbidity and mortality in modern society. Brain tumors, including gliomas, astrocytomas and glioblastomas, constitute a relevant and unsolved clinical problem and the treatment of brain cancers are major challenges.[1] A successful therapy for CNS disorders crucial milestones: (1) crossing the BBB into the brain, (2) reaching the specific cells to which it is directed, and (3) performing its ameliorative function there. Further, any therapeutic must have a safety profile that supports chronic dosing. The BBB allows the creation of a unique extracellular fluid environment within the central nervous system (CNS) whose composition can, as a consequence, be precisely controlled.

The extracellular fluid compartments of the CNS comprise the brain and spinal cord parenchymal interstitial fluid (ISF) and the cerebrospinal fluid (CSF), contained within the ventricles of the brain and the cerebral and spinal subarachnoid spaces. The structural BBB is created by the cerebral endothelial cells forming the capillaries of the brain and spinal cord. The fact that dye injected intravenously into animals stains all body tissues except the brain has been known for more than a century; this observation shows that the brain capillaries prevent molecules from entering the intact central nervous tissue. Thus, the concept of the blood-brain barrier (BBB) was established. The BBB is a result of the endothelial cells of normal brain capillaries, which have many unique properties.[2-7] Endothelial cells of brain capillaries have fewer pinocytotic vesicles and more mitochondria than those of capillaries elsewhere in the body, and the capillaries themselves lack fenestrations and inter endothelial passages Various transport mechanismsat the BBB have been explained for the transport of these substances (Fig. 1). These transport systems mainly operate in the luminal and abluminal membranes, i.e. from both blood-to-brain and brain-to-blood directions. But the blood-to-brain transport system is of considerable interest in drug delivery for targeting of drug molecules into brain as compared to brain-to-blood transport system.

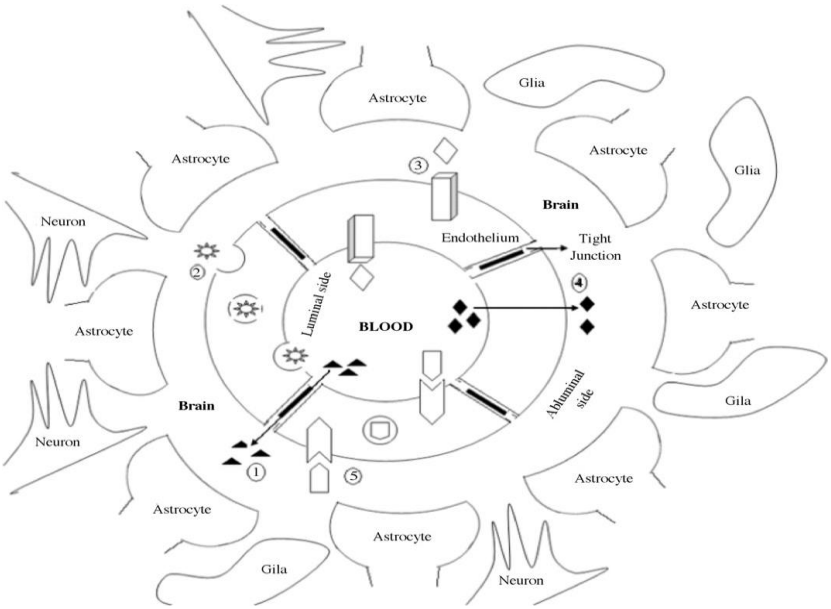

Fig.1

In addition, some regions of the CNS called as circumventricular organs (CVO) are present adjacent to the ventricles of brain where BBB capillary endothelial tight junctions are absent. These brain sites are unique in terms that they are highly vascularised as compared to other brain regions and lacks BBB because the capillary system supplying the CVOs contains fenestrated endothelial cells instead of epithelial tight junction.[8-10] Examples of such areas include choroid plexus, pineal gland, neurohypophysis, median eminence, organosum vasculosum of lamina terminalis, subfornical organ (SFO), area postrema of the chemoreceptor trigger zone (CTZ) and nucleustractus solitarius (NTS). These sites require intimate contact to closely monitor the composition of the blood and to respond accordingly. Compared to the area of tight BBB capillaries, the relative surface area of the capillaries of CVOs is very less (5000:1) which enables CVOs not to allow a significant diffusion of substances into the CNS.

Physicochemical properties of Brain delivery: The majority of drugs that are used to treat CNS disease have a molecular weight between 150 and 500 Daltons and log octanol /water partition coefficient between 0.5 and 6.0. It is generally assumed that charged molecules cannot readily penetrate the BBB thus, for a drug that is partially ionized at physiological pH 7.4, it is the uncharged fraction that determines the diffusion gradient across the BBB and forms the driving force for any passive diffusive movement of drug. Relatively small chemical modifications to a molecule may enhance the circulatory half-life and increase the area under the curve in plasma. This increase in half-life may stem from a reduced peripheral

distribution volume or resistance to enzymatic hydrolysis in the circulation. In addition, several highly lipid soluble molecules whose CNS penetration would be expected to be significant do not have the expected high BBB penetration. These drugs were initially thought to be excluded from the CNS by virtue of their physical properties, as they are generally all bulky molecules of high molecular weight. However, it is apparent that not all of the lipid-soluble molecules that are excluded from the CNS share these same characteristics.[11] It is now clear that these drugs are substrates for the ABC group of efflux transporters mentioned earlier, which continually hydrolyze ATP and are able to extrude drugs from the cerebral capillary endothelial cells and the CNS into blood against a concentration gradient. These ABC transporters include Pgp (Pgp /ABCB1), multidrug resistance proteins (MRP/ABCC1–12), and breast cancer resistance protein (BCRP/ABCG2).[12]

BBB transport system: 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. Cells have different receptors for the uptake of many different types of ligands, including hormones, growth factors, enzymes, and plasma proteins. It occurs at the brain for macromolecular substances, such as transferrin, insulin, leptin, and IGF-I & IGF-II, and is a highly specific type of energy dependent transport.[13-15]

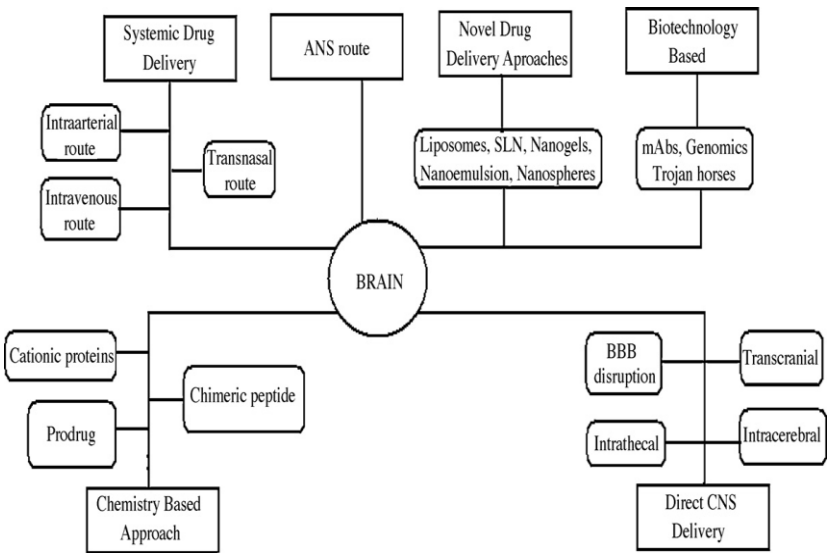

Fig.2

STRATEGIES FOR ENHANCED CNS DELIVERY

1. Direct systemic delivery

Several strategies have been studied shown in Fig. 2 for effective clinical outcome for different CNS conditions.

a. Intravenous delivery

It delivers drugs directly into general circulation by avoiding its first-pass metabolism and has potential to transport drugs to the 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.[16] 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.

b. Olfactory route

Delivering drugs for systemic action as the drug directly reaches to blood by crossing the nasal mucosa. The highly permeable nasal epithelium allows rapid drug absorption to the brain due to high total blood flow, porous endothelial membrane, large surface area and avoidance of first-pass metabolism. The olfactory region of respiratory region[17], 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. 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 achieving very rapid cerebrospinal fluid levels.

c. Intra-arterial delivery

The basic mechanism behind the bioavailability of drug in brain may be due to movement of drug in capillaries, then to choroid plexus epithelium and finally reaching CSF or by falling into arterial blood and then going to CSF through white matter and perivascular pathway.[18]

2. Direct CNS delivery

a. Intracerebral delivery

Intracerebral delivery involves delivery of drug directly intoparenchymal space of the brain. The major problem with bolus injection is slower movement of compounds within the brain due to the limited diffusion coefficient.[19] 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 brainIntracerebral implants are devices for controlled release of drugs at the target site in the brain. Polymer depots have been used for the delivery of drug into cerebral environment in the tumor cavity of the brain having drug being present inside the polymer matrix as a core material. It offers sustained release of drugs by the biodegradation of polymer.[30-31]

b. Trans cranial drug delivery

This route is best suited for meningioma treatment and metastatic cells of CSF[20] as it distribute drugs mainly into ventricles and subarachnoid area of brain. The major disadvantages are the chance of causing subependymal astrogliatic reaction due to high drug exposure at the ependymal surface of brain.

c. Intrathecal delivery

Intrathecal route involves delivery of neurotherapeutic agents to brain by direct administration of drugs through intrathecal route into cisterna magna of brain. Intrathecal route is best suited for drug delivery for treatment of spinal diseases and disseminated meningeal diseases but not for large parenchymal diseases like parenchymal tumors such as glioblastoma.[21]

d. BBB disruption

Drug substances are directly delivered to CNS by the use of certain chemical substance or by the application of energy like ultrasonic waves or electromagnetic radiations externally which helps in the opening of tight junctions and provides successful entry of drugs into the brain . In the first method various chemical substances are used which have hyperosmolar nature, i.e., have higher hypertonicity or osmotic pressure.[22] Hypertonic solution causes opening of tight junctions due to higher osmotic pressure, which leads to shrinking of endothelial cells, by which disarrangement of extracellular proteins occurs and finally entry of drug takes place paracellularly. Various osmotic substances have already been tested and amongst these

mannitol has been found to be effective and safe . It is administered by intracarotid arterial infusion along with drug substances with the help of cannula.

Mannitol has been used for several years for treating brain tumors where barrier is opened for 30 min when 25% solution of drug is allowed for 30 s . Similarly, enhanced methotrexate delivery to the CNS has been attained by intra-arterial administration combined with osmotic disruption of the BBB by mannitol compared with simple intra-arterial or intravenous administration several other substances have been found that can alter the BBB permeability including bradykinin, alkylglycerols.

Secondly, BBB disruption can be achieved by the application of ultrasound[23] and electromagnetic radiation. The important advantage of this approach is its specificity for targeting to a specific area of brain. There are three basic mechanisms proposed for describing the path of entry of drug molecules into brain using this method. Firstly the temperature of ultrasonic waves induces thermal lesions leading to alteration of permeability and generalized opening of BBB. The normal dose of ultrasonic energy applied is very low, approximately around 200–300 kHz. Secondly the cavitation effect produced by the injected fluid leads to formation of small air filled cavity in barrier's luminal membrane making the entry of drugs easier to brain and the third possible mechanism describes the formation of micro-bubbles by ultraultrasound contrast agent. This method is now used mostly as diagnostic tool as a contrast agent for imaging the brain microenvironment as well as tumors.[26-29]

Permeation enhancers such as surfactants, sodium dodecyl sulphate, Dimethyl sulfoxide, polysorbate, PEG-Hydroxy stearate.[32]

3. **Prodrugs and chemical delivery systems**

a. Inert alternatives of original API to get a product of large bulky structure which has neither biological toxicity nor activity.[24] These prodrugs give active moiety at the site of action, in brain due to the enzyme specific nature of them.Whenever these moieties reach the brain through blood, the enzymes present on the surface of BBB help in metabolism of prodrugs to give active agents, which then cross the BBB and attains concentration in brain. These are several approaches such as

- Prodrug "Lock-in" mechanism for drug targeting[33]
- Cyclodextrin complexes for drug delivery
- Biotin-avidin conjugated system for drug delivery
- Antibody directed enzyme prodrug therapy (ADEPT)

b. Chimeric peptides

The word "chimeric" obtained from the Greek word chimera means an animal having body of lion and head of human. The conjugated vector maybe endogenous peptides, monoclonal antibodies (mAbs), modified proteins, peptidomimetic antibodies. These chimeric peptides are formed by covalent binding of a BBB non-permeable neuropeptide with the vector. For example, insulin and transferrin are the two circulating peptides which undergo transcytosis by their insulin and transferrin receptor present at BBB.[25]

c. Cationic proteins

It is the best suited technique for delivering proteins and peptides with a basic isoelectric point to the brain. Hence this method provides an additional advantage for delivering them by making them charged into cationic form, which can easily enter brain by electrostatic interaction with anionic functional groups present on brain surface. After cationization they easily enter by using the transcellular adsorptive-mediated endocytosis pathways.[26]

4. Novel approaches for brain targeting

a. Liposomes

Related strategy for achieving transit of neuropharmaceuticals across the BBB uses the attachment of immunoreactive moieties to liposomes. The formation of immunoliposomes designed to target specific tissues has been known for two decades.[35-37] They possess advantages of carrying hydrophilic, lipophilic as well as amphoteric drug molecules either entrapped inside it or on its micellar surface. The brain distribution of long circulating liposomes can be modulated by conjugation of appropriate targeting vectors.

b. **Nanoparticles**

Nanosystems employed for the development of nano drug delivery systems in the treatment of CNS disorders include polymeric nanoparticles, nanospheres, nanosuspensions, nanoemulsions, nanogels, nano-micelles and nano-liposomes, carbon nanotubes, nanofibers and nanorobots, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugates (LDC).

5. **Biotechnology based approach**

a. Monoclonal antibodies for targeting

b. **Application of genomics in brain drug delivery**

Possible methods for delivery of gene therapeutics specifically to the human brain include invasive craniotomy, cationic-liposome–DNA complexes, or viral vectors; but each technique has some limitations.[34] Gene therapy would ideally use a non-viral formulation, intravenously administered, with widespread gene expression throughout the brain, and specific localization to the brain with no expression in peripheral tissues. In theory, gene expression in the brain could be altered with the targeting techniques discussed above, in combination with gene promoters specific to particular cells.

c. Molecular Trojan Horses (monocytes) for brain targeting

6. Drug delivery through autonomic nervous system

The autonomic nervous system has now came into existence as an ideal route for delivering drugs to brain.

CONCLUSION

Further physicochemical modification of these more potent drugs may provide a small but vital increment in their CNS permeability, which results in a very significant increase in the therapeutic index. It is armed with this improved knowledge that drug development can move into a more informed and rational phase aimed at optimizing drug design for delivery to the CNS. An effectual advance for achieving capable drug delivery would be to judiciously develop delivery strategies based on the understanding of their interactions with the biological environment, changes in cell receptors that occur with progression of disease, mechanism and site of drug action, multiple drug administration, and pathobiology of the disease under consideration. The search for new methods of achieving BBB transit of specific brain-targeted compounds is just beginning, but the remarkable progress of the past decade suggests that the ability to deliver BBB-impermeable agents across the brain endothelium is an attainable goal.

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