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REVIEW ON NOVEL APPROACHES FOR TARGETING DRUGS TO THE BRAIN

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ABSTRACT

Human Brain is very delicate organ and it act as vital controlling unit of body and hence it is strictly protected by nature to shieldregular brain function. Blood Brain Barrier [BBB] is among the main barriers which restrict entry of different drugs into the brain. And because of BBB it is more difficult to treat several diseases of brain like Alzheimer's disease, Parkinson's diseases, dementia, mood disorders, AIDS and several bacterial infections. Therefore it is necessary to employ novel approaches for treatment of disease of brain. These novel approaches will target brain in effective way. The current review encompasses various barriers for delivery of drug into brain along with several novel approaches which can be used for targeting drug to the brain like use of prodrug, use of nanotechnology based products, by use of different carries like liposome, microspheres, nanoemulsion, polymeric micelles and dendrimers.

KEYWORDS: Brain, Blood Brain Barrier, Alzheimer's disease, Nanoparticles, Liposomes.

INTRODUCTION

Brain is the most important, most delicate organ of human body. It is crucial commanding unit of human body. Therefore to protect it, nature has created some barriers between blood flow and brain. Unfortunately the barrier which was made to protect the brain also became roadblock for the treatment of various CNS disorders. Though brain is highly vascular organ, drug targeting to brain is very challenging. Many CNS disorders are unsuccessful in treating because drugs cannot be effectively delivered to the brain. There are different physiological barriers separatingthe brain from its blood supply controlling the transport of compounds.

One is the blood–brain barrier [BBB], second is blood–cerebrospinal fluid barrier [BCSFB] and third one is arachnoid barrier.[1][2] 100% of large size molecules are unable to cross BBB while 98% of small size molecules do not cross BBB. Only little group of drugs which are having more lipid solubility and molecular weight less than 400 to 500 Daltons are able to cross BBB.[3] Various barriers which appose transfer of drug into brain are discussed in short.

Blood Brain Barrier [BBB]: It is well known fact thatblood brain barrier is a unique barrier that separates brain from rest of circulating blood. This barrier does not allow entry of harmful toxic substances into the brain for the protection of brain. This barrier consists of blood capillaries that are structurally different from other blood capillaries which are present in other organs of body. Capillaries in other tissues allow free exchange of substances across the cell but capillaries in brain limit transport of substances into brain.[1] Blood Brain Barrier forms a tight junction in between endothelial cells in brain capillaries which prevent transport of unwanted substances, toxic molecules and pathogens into the brain.[4]

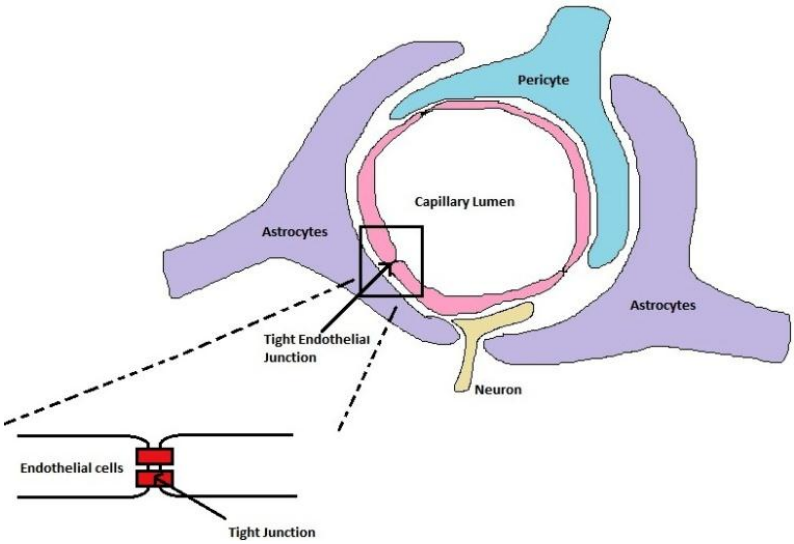

Fig. 1: Structure of Blood Brain Barrier.[5]

In spite of such strict gate keeping, BBB allows entry of certain vital nutrients like glucose, proteins, peptides and minerals in brain through multiple endogenous transports.[1][5]

Blood–Cerebrospinal Fluid Barrier [BCSFB]

This is another type of barrier between circulating blood and brain. This barrier separates cerebrospinal fluid which is present in brain and circulating blood. This barrier dose not imposes much problem in drug delivery because it is having much smaller area(5000 fold smaller) than blood brain barrier. Physiologically, the BCSFB is present in the epithelium of

the choroids plexus, which is arranged in a manner that restricts the way of molecules and cells into the CSF. The choroid plexus and the arachnoid membrane operatemutually at the barriers between the blood and CSF. The arachnoid membrane is generally resistant to hydrophilic substances.[6-10]

Blood-Tumor Barrier

The blood-tumor barrier, similar to blood-brain barrier, is located among brain tumor cells and microvessels. A malignant tumor results in many changes that contribute to specific pathological disruptions of the BBB. Targeting CNS tumor becomes even more difficult when target is CNS tumor. Occurrence of the BBB in the microvasculature of CNS tumors has clinical significance.[11,12]

Drug delivery to cancerous cells is compromised by a mixed distribution of microvasculature all through the tumor interstitial, which leads to spatially unpredictable drug delivery.

When tumor size grows, trans vascular blood exchange decreases, intra-capillary distance increases, accumulation of fluid also increases which causes less permeability to drugs than normal brain endothelium.[13]

Apart from these barriers various other factors also affect transfer of drug as follows;

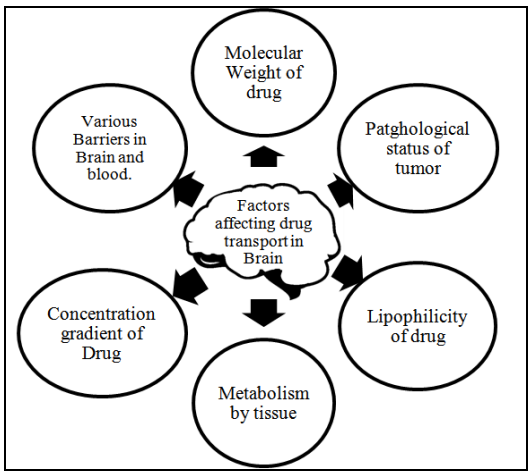

Fig. 1: Various difficulties for delivery of drug to the brain.

Approaches for targeting drug to Brain

Various approaches are used to target drug to the brain. These methods are basically classified into two group, Invasive method and non-invasive method. In invasive method neuroprotective barrier between blood and brain is opened or disturbed by methods like

ultrasound, osmotic pressure difference or by vasoactive agents like bradykinin. In non-invasive method drug transport across BBB is carried out by using various endogenous transport mechanisms or by using various transporter systems.

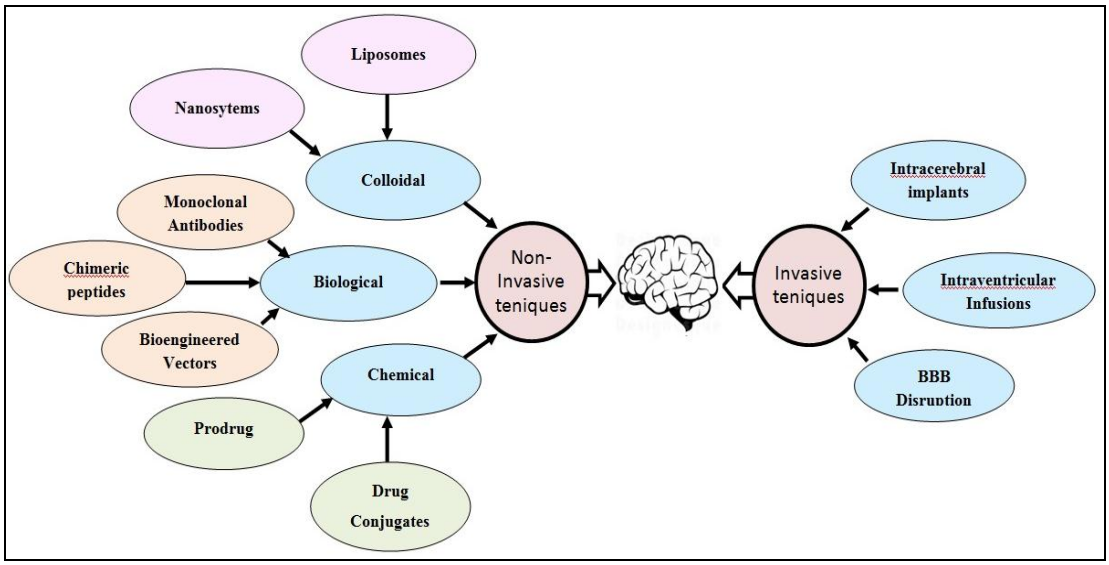

Fig. 2: Various approaches used for delivery of drug to brain.

Various Pharmaceutical technology based systems like liposome or Nanoparticles are used to for enhancing transcellular permeability ofvarious pharmacological active compounds and macromolecules across BBB. Apart from these systems, systems like dendrimers, micelles, Nanoparticles are attempted for targeting drug molecules to brain.[13]

1]Nanoparticles: Nanoparticles are being used for delivery of drug to precise target sites of body and one of the widely used approach for delivery of drug to brain. Nanoparticles are defined as solid particles having size range of 10-1000 nanometers. The drug is either entrapped in polymeric system called as nanospheres or encapsulated in polymeric structure called as nanocapsules(fig. 3) or nanosize particles suspended in solvent system called as nanosuspension or oily liquid drug dispersed in aqueous solvent called as nanoemulaion.[14] Particle Size, Surface properties and release pattern of pharmaceuticals can be controlled by designing Nanoparticles. Nanoparticles are able to diffuse through various biological membranes which benefit to cross BBB and deliver drug to Brain. Also another advantage of nanoparticle isimprovement in bioavailability of poorly absorbed drug.[15] Some studies also indicate that because of Nanoparticles, drug retention inside tumor is prolonged causing reduction in tumor growth.[16-17] Mechanism behind opening of barriers by nanoparticles is not known exactly. Some studies suggest that nanoparticles enter into brain via small size

mediated endocytosis.[18] Other mechanisms are reported by which nanoparticles achieve maximum drug concentration in brain like improved retention of drugs in brain blood capillaries collectively with an adsorption to capillary walls as elevated concentration gradient enhance transport, increasing BBB membrane permeability, opening of tight junctions connecting cells of endothelium, restraining the p-glycoprotein efflux system.[19]

Magnetic nanoparticle is recent technique used for targeting drug molecule into tumour cells present in brain. The nanoparticles having magnetic properties are called as MNP (Magnetic nanoparticles). These MNPs can create temporary pores into membrane of cell by process called as magnatoporation which improves targeting of nanoparticle into brain. These MNPs can be utilised for therapeutic or diagnostic purpose as well.[20]

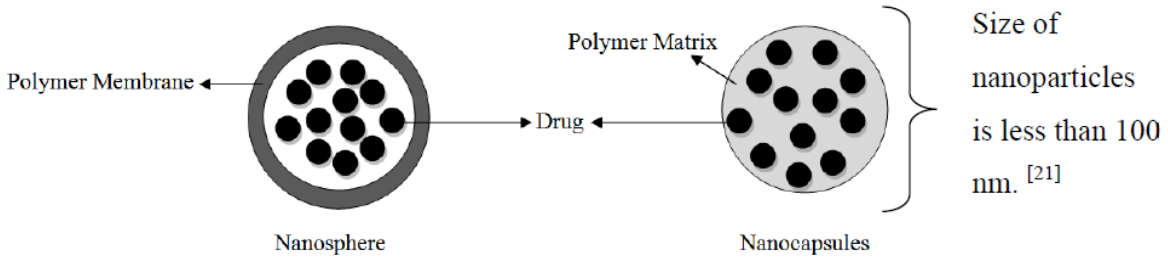

Fig. 3: Nanospheres and Nanocapsules.

2] Liposomes

Liposomes are nano or micro size capsules consisting of aqueous compartment surrounded by lipid bilayer membrane. Size of liposome ranges from 0.05 to 0.5 micrometer.[22] Liposomes were discovered in early 1960 and since then this is highly explored carrier system for drugs for treatment of neurological diseases.[23] Liposomes are made up of naturally occurring biocompatible substance such as phosphatidylcholine derived from soybean lecithin hence they are non-toxic and non-immunogenic. Liposomes are used for encapsulation and cotransportation of hydrophilic as well as hydrophobic drugs.[24] Liposomes are widely investigated for transport of various pharmacologically active agents like antineoplastic, vaccines, chelating agents and genetic material.One of the major problem associated with liposome was stability but due to recent advancement this problem can be overcome. On the basis of number of bilayer present in liposome it can be classified as small unilamellar vesicle, large unilamellar vesicle and multilamellar vesicle.[22] Drugs like doxorubicin, daunorubicinhave been approved in liposome based formulation for clinical trials. Small hydrophobic molecules such as rivastigmine, tacrine, resveratrol, donepezil, curcumin are

formulated in the form of liposomes. The main problem associated with these drugs that is their poor water solubility can be overcome by formulating these drugs in liposomal form for treatment of neurodegenerative diseases.[25] Liposomes also overcome various disadvantages related to conventional formulation such as low bioavailability and non-specificity.[26]

There are a number of ways by which liposomes allow drug transportation across the BBB, like carrier-mediated transport, passive transcellular diffusion, transferring receptor and insulin receptor-mediated transcytosis, absorptive-mediated transcytosis, cell-mediated transcytosis, and efflux pumps.[27] Receptor mediated transcytosis is the mainly considered transfer path for the liposome delivery system. With the help of transferrin (TfR) or insulin receptors (IR) liposomes with no trouble bypass through the BBB and take therapeutic drugs into the CNS.[28] Likewise, liposomes can also be attached to monoclonal antibodies of glial fibrillary acidic protein (GFAP) to bypass the BBB. A recent study accounted a liposomal nanohybrid cerasome formulated from polysorbate 80 as a P-gp inhibitor to increase the BBB permeability of curcumin in the treatment of PD, with notableresult.[29]

In recent years, ferromagnetic liposome based drug delivery system has been formulated to increase therapeutic efficacy. By application of external magnetic field, Fe_3O_4 assisted liposomes can be targeted to the site which show improved pharmacokinetics profiles. The Fe_3O_4-modified nimodipine liposomes were found to successfully cross the BBB.[30]

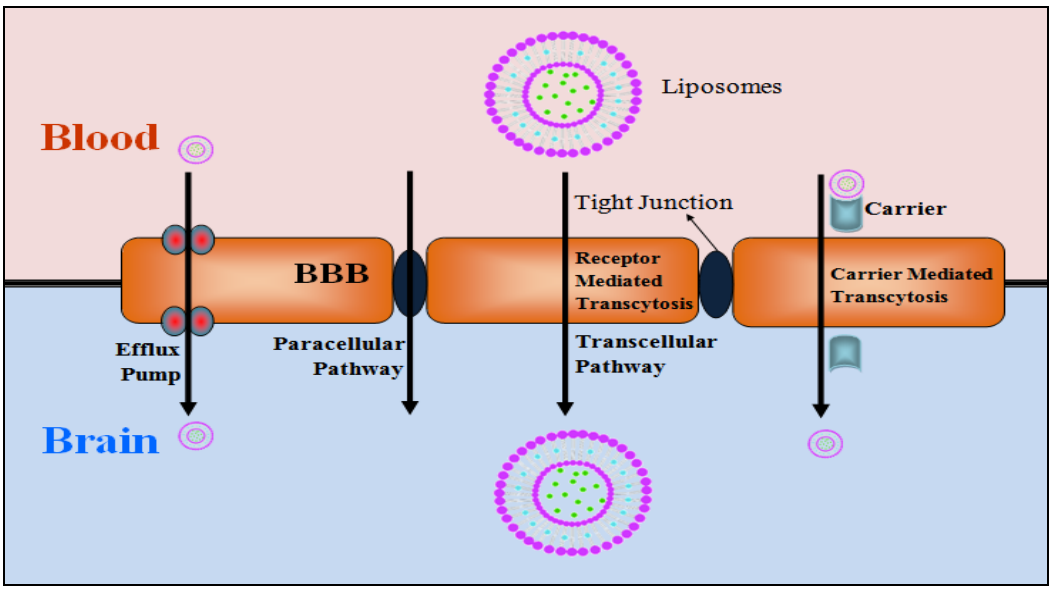

Fig. 4: Various transport pathways of liposome through BBB.

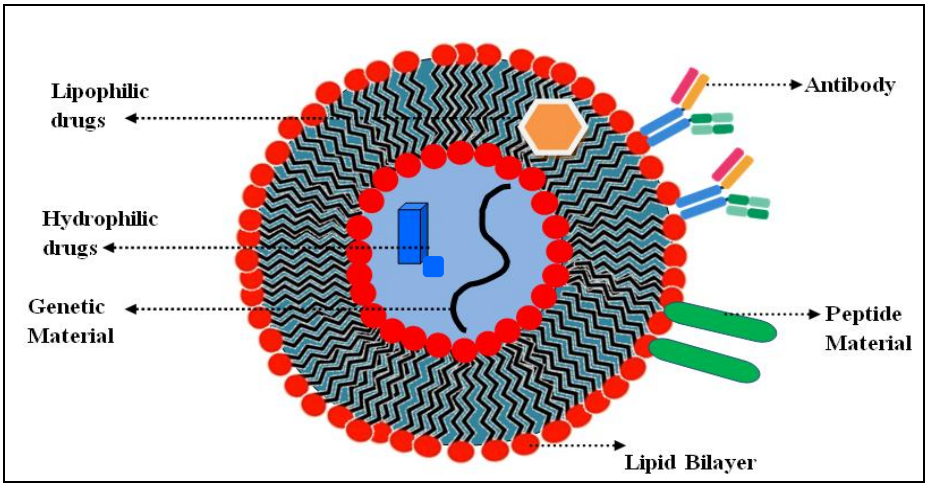

Fig. 5: Concept of liposome for delivery of drug into brain.

3] Dendrimers

Dendrimers are nanosized macromolecules known by hyper-branched spherical structure and widely utilized as drug delivery system. In contrast with traditional polymeric nanovehicles, dendrimers are of monodispersity and have known chemical structures. Additionally, the specific structure of dendrimers gives them addition advantage of flexibility to load therapeutic drugs by either covalent conjugation or electrostatic adsorption.[31]

Dendrimers consists of mainly three parts, 1st one is a central core made up of single atom or group of atoms, 2nd is building blocks known as generations which are attached to central core and 3rd part is functional groups present on surface (Fig. 6).

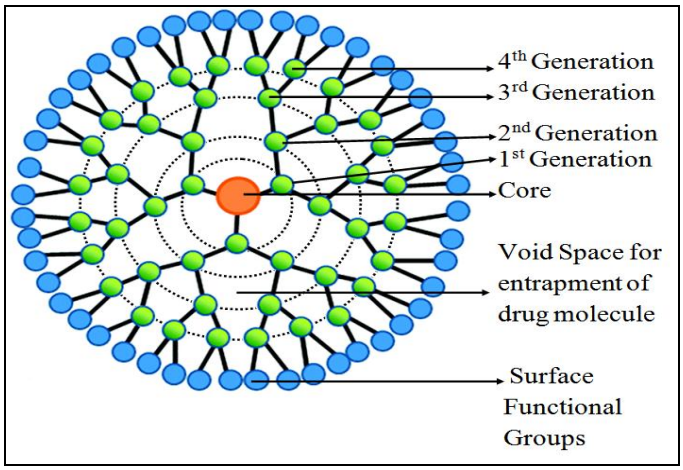

Fig. 6: Structure and generations of dendrimers.

Dendrimers are mostly synthesized by using two approaches. First method known as divergent method, dendrimers are constructed from core to periphery and second method

known as convergent method in which dendrimers are constructed from periphery to core.[32] The exterior groups may have positive, negative, and neutral charges, which is important in using appropriate dendrimers as preferred drug delivery transporter.[33] To target drug into brain by using dendrimers drug molecules can either be physically encased into the internal cavities of dendrimer molecules or chemically conjugated to the surface functional groups. There are various strategies through which drug molecule can be targeted into brain. Among them some are as follows. Polyamidoamide [PAMAM] dendrimers can be targeted into brain by transferrin receptor targeting. Low density lipoprotein receptor-related proteins [LRP1 and LRP2] are multifunctional forager receptors expressed on the BBB. They have a capability to bind to a range of molecules and make them cross the BBB. Dendrimers can bind to these receptor and can cross BBB. Another mechanism of targeting drug by using dendrimers is through glucose transporter system. Glucose transporter system is utilized for transfer of glucose into brain. This transporter system can be utilized for targeting drug into brain with help of dendrimers.[34]

4] Prodrug approach

Prodrug is the chemical moiety which undergoes biotransformation before showing therapeutic activity. The term Prodrug was introduced in 1958. Prodrug is also called as pro agent.[35] Prodrug is the bioreversible derivative of drug molecule along with promoiety which undergo chemical or enzymatic transformation inside body into active form before showing pharmacological activity (Fig.7)

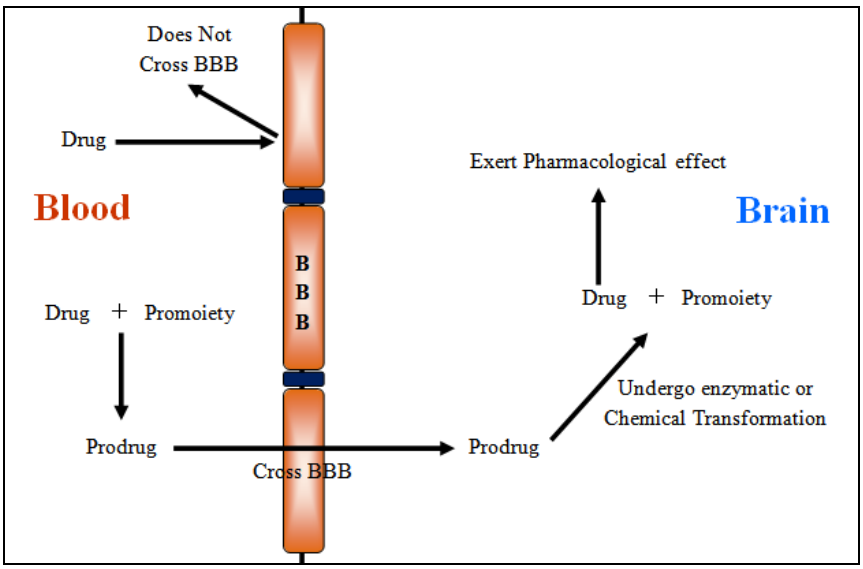

Fig. 7: Illustration of Prodrug concept.

The major reason behind Prodrug design is to overcome various physicochemical, pharmaceutical, pharmacokinetic and biopharmaceutical limitations of parent drug molecule.[36] One of the reason behind conversion of drug in Prodrug is to overcome disadvantage of parent drug of failing to cross BBB. Converting such drug in Prodrug can overcome this problem. By application of this concept usefulness of drug molecule can be enhanced without damaging pharmacological properties of parent drug.[37] The classical example of this approach is of Morphine. Morphine does not cross BBB easily but its acetylated product Heroin can easily cross BBB which further in brain by hydrolysis generated Morphine in brain. Various chemical modification approaches such as esterification of hydroxyl group, amidation of hydroxyl or carboxylic group may increase lipophilicity of drug and enhance its transport through BBB.[38]

5] Molecular Trojan Horses

As large molecules do not cross BBB hence proteins, peptide, enzymes and monoclonal antibodies are not much tried for brain diseases. Hence a new solution for delivery of such drug is by using genetic engineered recombinant fusion proteins. These big molecules are attached to a molecular Trojan horse. These molecular Trojan horses are the second peptide or peptidomimetic monoclonal antibody which binds a precise receptor of the Blood Brain Barrier. These Trojan horses delivery the big molecules across BBB into Brain by receptor mediated delivery of the combination of protein across the BBB to exert pharmacological effect. Various pharmacological agents such as Peptides, recombinant proteins and antisense agents are delivered successfully across BBB hence this delivery have generated the intended CNS pharmacological effects.[39] Currently delivery of drugs across BBB based on molecular shuttle is under investigation.

6] Viral vectors

Nucleic acid containing cells can be naturally infected by viral vectors. From two decades viral vectors have been tried for gene delivery to the patients suffering from various neurological diseases. Various viral vectors such as Lentivirus, herpes simplex virus, adenovirus and adeno-associated virus[AVV] have been successfully utilized for transduction into brain. Efficiency of transfection of viral vectors is very high.[40] But here are several limitations of using viral vector for drug delivery such as high cost of production, difficulty in manufacturing and the most concerning is the toxicity of viral vectors. During clinical trials of viral vectors death of patients have occurred which raises concerns about its safety as a

drug delivery system.[41] Hence before clinical trials safety profile of viral vectors should be established. Among the above mentioned viruses adeno-associated virus has shown safetyin humans as well as its ability for gene delivery in the brain.[42] Thus, AVV vector is a prominent vector used in current clinical trials of gene therapy for brain diseases.

7] Brain targeting via nasal route

Intranasal drug delivery is not very convenient but it is explored as one of the potential route for brain targeted drug delivery. Drug administered through nasal route is absorbed into the systemic circulation throughtranscellular and paracellular absorption, carrier-mediated transport, and through trancytosis mechanism.[43] Drug administered deep into nasal cavity causes direct transmission of drug into brain via olfactory pathway. This pathway consists of olfactory neurons which transfer drugs from olfactory mucosa to the brain. It is slow process of drug transport. Another fast way of drug transportation is through olfactory epithelium pathway.[44] The route through which drug is transferred into brain is from nasal cavity to perineural space and directly into brain.[45]

8] Nanoemulsion: The nanoemulsions are heterogeneous thermodynamically stable nanosized dispersion of water-in-oil or oil-in-water with emulsifying agent.[46] Nanoemulsions can be utilized for delivery of both hydrophilic as wellas lipophilc drugs. Nanoemulsion with suitable surface functionalization ligand makes possible the permeation of nanoemulsion via recptor mediated transport. The lipid phase of Nanoemulsion is made up of biocompatible oils such as egg phosphatidylcholine, peanut oil, flaxseed oil, sunflower oil, hemp oil, fish oil, wheat germ oil, etc. Another advantage of Nanoemulsion is size of dispersed phase is less than 200 nm which makes it promisingtransporterstructure for brain targeting.[47]

In geneal nanoemulasions are used through nasal route for direct nose-to-brain delivery of drugs.

In 2015 Tan et al prepared parenteral nanoemulsion for brain targeting of carbamazepine for treatment of seizure and evaluated its pharmacokinetic efficiency. The study indicatedthat drug used in free form has lower pharmacokinetic profile and higher side effects as compared to drug in nanoemulsion form which show potency of this system for brain targeting.[48]

The research work carried till date indicates nanoemulsion in mucoadhesive form is more effective for targeting brain through nasal route as well as parenteral route. Study shows nanoemulsion is less adverse effect, improved therapeutic potency and patient friendly technique to access brain.[49]

CONCLUSION

Targeting drug to the brain is not simple mission. The security mechanism of Blood Brain Barrier makes it difficult to transport drug into brain. But it is necessary to transport drug across BBB into brain for treatment of various neurological disorders like Alzheimer's disease, Parkinson's diseases, brain tumors etc. By using some endogenous transporter mechanism, recptor mediated transport, efflux pump mediated transport it is possible to cross BBB. For this purpose various methods like nanoparticles, nanoemulsion, dendrimers, molecular Trojan horses, viral vectors, prodrugs and nasal route are being explored and will be explored in future also.

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