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Review Article

NOVEL APPROACHES FOR BRAIN TARGETTING

Monika Kamble[1] , Archana Gawade

1. Department of Pharmaceutics, Dattakala Shikshan Sanstha, Dattakala College of Pharmacy, (Affiliated to Savitribai Phule Pune University), Swami Chincholi, Daund, Pune, Maharashtra, India-413130.
2. Managing Director, Elite Institute of Pharma Skills, Pune

Address for correspondence:

Monica Kamble, Department of Pharmaceutics, Dattakala Shikshan Sanstha, Dattakala College of Pharmacy, (Affiliated to Savitribai Phule Pune University), Swami Chincholi, Daund, Pune, Maharashtra, India-413130.
E-mail- monikakamble8600@gmail.com

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ABSTRACT:

Human Brain is a very delicate organ and it acts as vital controlling unit of body and hence it is strictly protected by nature to shield regular brain function. The Blood Brain Barrier (BBB) is one of the key barriers that prevents dangerous chemicals and medications from entering the brain. While the BBB is a thick brain barrier that prevents medicine from reaching the CNS, making it difficult to treat a variety of brain illnesses such as Alzheimer's, Parkinson's, dementia, mood disorders, neuronal-AIDS, and CNS tumors/cancers. As a result, fresh methods to the treatment of CNS brain illness are required. Novel techniques, such as magnetic drug-targeting and drug carrier systems, will effectively target the brain. The total incidence rate for CNS disease has shown that over 1.5 billion individuals suffer from central nervous system illnesses. The existence of the Blood-Brain Barrier, which has a propensity to hinder medication distribution and is a significant hindrance to the development of CNS therapies, is the most worrisome truth regarding drug delivery to the CNS. Many medications that are hydrophilic in nature, such as neuropeptides, may be able to cross through the blood brain barrier with ease. The major considerations for CNS medication development are the net quantity of administered medicine (medicinal agent) and its capacity to acquire access to the relevant target locations. Many novel developing techniques, such as biomaterials and colloidal nanoparticles systems, have

been created to transport medications into the CNS by crossing the Blood-Brain Barrier (antibodies, liposomes or nanoparticles).

KEYWORDS: Blood-Brain barrier, CNS disorders, Drug delivery to brain, Nanotechnology, Colloidal drug carriers.

INTRODUCTION:

The brain is a delicate organ that is separated from general circulation by the presence of a relatively impermeable Blood-Brain Barrier (BBB). The Blood-Brain Barrier keeps the brain in a state of homeostasis by preventing foreign bodies and a variety of molecules from entering. As a result, a number of promising molecules fail to reach the target site and produce an in vivo response. Despite this, the brain easily absorbs lipid nanoparticles due to their lipophilic composition. Lipid nanoparticles are less toxic and more suitable for brain targeting due to their bio-acceptability and biodegradability.

The brain is the most essential organ in the human body and serves as the body's controlling unit. As a result, nature has developed certain barriers between blood flow and the brain to safeguard it. Unfortunately, the same barrier that was put in place to protect the brain has also become a hurdle in the treatment of different CNS illnesses. The blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier (BCSFB), and the arachnoid barrier are the three. Large molecules (molecular weight more than 600 Daltons) could not penetrate the BBB; hence this could not be permitted. Only a few medicines with a high lipid solubility and a molecular weight of less than 400 to 500 Daltons may penetrate the BBB [1]. The passage of numerous hazardous substances to the CNS has been prevented by BBB.

Despite the fact that the brain is a highly vascular organ, medication targeting it is very difficult. Many CNS illnesses are difficult to treat because medications cannot reach the brain efficiently. The movement of chemicals is controlled by several physiological barriers that separate the brain from its blood supply. Direct injection of medicines into the central nervous system may produce focused activity in the CNS [2]. Because of its tenacious obstruction effect, the blood-brain barrier may significantly reduce the action of a wide range of medications (e.g., antibiotics, antineoplastic treatments, and Neuropeptides-CNS stimulant pharmaceuticals) [3]. According to several recent research, almost 100% of big molecule medications and 98 percent of small molecule pharmaceuticals do not penetrate the blood-brain barrier [1]. For the treatment of brain diseases, several techniques with improved pharmacodynamic effects have been devised [4]. The two key sectors where progress is needed for drug delivery to the brain are drug discovery and drug delivery technology [5]. The nanoparticles drug delivery system (NDDS) is one of the most modern methods for delivering therapeutic molecules directly into the brain, and it has been shown to be particularly effective against a variety of CNS illnesses [6]. The nanoparticle medication delivery technology has a lot of advantages (NDDS).

The development of biodegradable materials and nanoparticle surface functionalization has enabled for novel therapeutic options, according to this opinion piece. The reasons why there are so few nanoparticle-

based drugs on the market or in late clinical trials are reviewed, as well as several novel techniques. Future problems in the realm of nanoparticles are also discussed.

Blood-Brain Barrier (BBB)

The blood-brain barrier is a well-known feature that divides the brain from the rest of the circulating blood. For brain protection, this barrier prevents hazardous poisonous chemicals from entering the brain. This barrier is made up of blood capillaries that are physically distinct from blood capillaries seen in other bodily organs. Although capillaries in other organs enable the unrestricted interchange of chemicals among cells, capillaries in the brain restrict substance transport. The blood-brain barrier is formed by endothelial cells in brain capillaries forming a tight junction that prevents undesirable chemicals, harmful compounds, and infections from entering the brain [4]. Despite the rigorous gatekeeping, the BBB permits important nutrients such as glucose, proteins, peptides, and minerals to enter the brain through numerous endogenous transporters (Fig. 1).

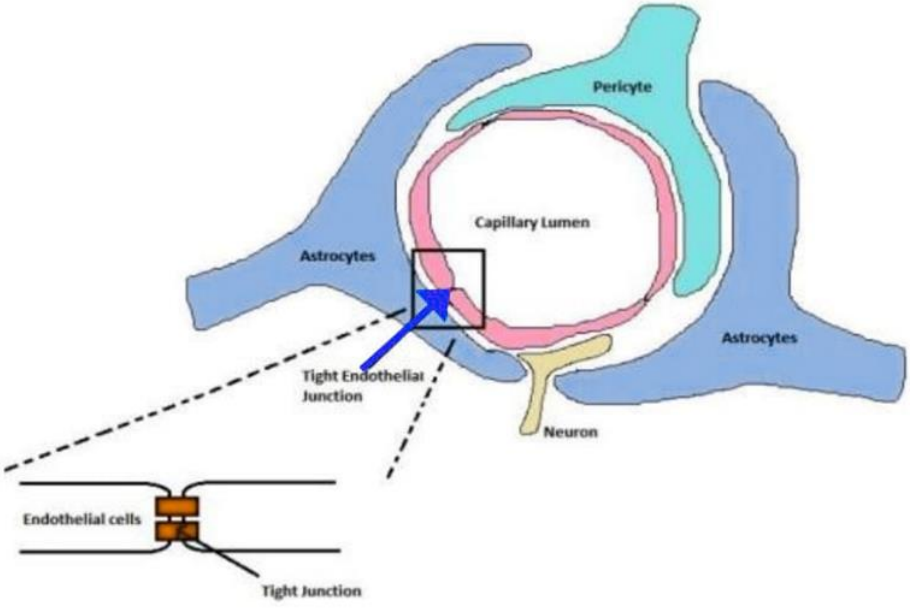

Fig. 1: Structure of Blood-Brain Barrier.

Blood–Cerebrospinal Fluid Barrier (BCSFB)

Another form of barrier between circulating blood and the brain is this one. The cerebrospinal fluid in the brain is separated from the circulating blood by this barrier. Because it has a considerably smaller area (5000 times smaller) than the blood-brain barrier, this barrier dosage does not offer a significant impediment in drug delivery. The BCSFB is found in the epithelium of the choroid's plexus, which is structured in a way that prevents molecules and cells from entering the CSF. At the blood-CSF barrier, the choroid plexus and the arachnoid membrane both works together. Hydrophilic compounds are often resistant to the arachnoid membrane [6-10].

Blood-Tumor Barrier

The blood-tumor barrier is found between brain tumor cells and microvessels, analogous to the blood-brain barrier. Many alterations occur as a consequence of a malignant tumor many of which contribute to particular BBB pathological disturbances. When the target is a CNS tumor, the task becomes considerably more challenging. The BBB's presence in the microvasculature of CNS malignancies has therapeutic implications [11,12]. Heterogeneous distribution of microvasculature across the tumor interstitial compromises medication delivery to malignant cells, resulting in a spatially unpredictable drug delivery system.

Intranasal Administration to Circumvent the Impact of BBB.

The blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier (BCSFB), and the arachnoid barrier all prevent medications from reaching CNS target areas. These barriers not only protect the CNS from viruses and hazardous chemicals but also serve as a conduit for blood–CNS communication. The BBB is found in the brain capillary endothelium. These brain capillaries have the biggest total surface area of any blood–CNS contact. As a result, the majority of CNS-active medicines reach the brain primarily via the BBB. There are two approaches to inhibiting drug trafficking across the BBB. Because tight junctions generate a strong link between adjacent endothelial cells, paracellular transport across the BBB is severely constrained and only achievable for smaller hydrophilic medicines that cannot readily penetrate cell membranes. The activity of efflux transporter proteins on the cell membranes of brain capillary endothelial cells, such as P-glycoprotein (Pgp) and multidrug resistance-related proteins (MRPs), may prevent transcellular transit of the BBB for more lipophilic medicines that may easily traverse cell membranes. Not all transporter proteins prevent medications from crossing the BBB; certain influx transporters actually help pharmaceuticals get to the brain. As a result, the BBB may play a major role in medication distribution into the CNS, as well as drug distribution to CNS target sites. The BBB's limiting influence on CNS medication distribution has spurred researchers to seek and develop innovative drug delivery strategies that can bypass it. The opening of tight connections between endothelial cells to promote the transport of hydrophilic medicines by paracellular diffusion is one method for bypassing the BBB. Opening tight connections, on the other hand, renders the

brain more exposed to undesired creatures and chemicals. Intracerebral implants and intraventricular infusions may also be used to bypass the BBB. Both of these medication delivery procedures are quite intrusive, and they are typically used only when no other options are available. As a result, safer, simpler, and less intrusive brain medication delivery strategies that circumvent the BBB are required.

Physiology of the Blood-Brain Barrier (BBB)

Most conventional chemotherapeutics cannot pass through the tightly controlled BBB [13]. Specialized endothelial cells [14, 15], which have particular features that produce an impenetrable barrier, limit transport across the BBB. The first is the existence of tight junctions, which restrict molecules from passing through the cell membrane. Occluding, tricellulins, claudins, and junctional adhesion molecules are the most common tight junction proteins. Second, endothelial cells in the CNS contain efflux transporters, which control substrate passage across the BBB [16]. Because efflux transporters are substrates for a variety of medications, drug build-up in the brain parenchyma is hampered. These efflux transporters are ATP-binding cassette (ABC) transporters, with multidrug resistance receptors (MDRs, ABCB), multidrug resistance proteins (MRPs, ABCC), and the breast cancer resistance protein (BCRP/ABCG2) being the most significant transporters [17]. MDR1 (ABCB1, P-glycoprotein [P-gp]), the most thoroughly studied ABC transporter in the brain, is involved in the efflux of a variety of medicines [18].

Pathology of the BBB/Blood–Tumor Barrier (BTB)

The control of the BBB is disrupted by the presence of a brain tumor, resulting in an altered BBB phenotype known as the blood–tumor barrier (BTB) [19, 20]. It is critical to characterize the BBB/BTB characteristics of various cancers in order to determine the efficacy of medication delivery for the treatment of primary brain tumors. The BBB/BTB of many primary brain tumors is addressed in the following paragraphs.

The BBB's Anatomy and Physiology

The BBB is made up of CNS endothelial cells that are connected by tight junctions to create a physical barrier that prevents hazardous chemicals from entering the brain. The circle of Willis (blood capillary network feeding the brain) is a complicated ramified arterial network formed by the joining of the internal carotid and vertebral arteries, which provides a rich blood supply to the brain parenchyma [21]. Endothelial cells specialize in preserving a continuous, non-fenestrated basal lamina while sustaining connection and material exchange between CNS neurons and neuroglia cells [22]. Astrocytes and pericytes are crucial for the growth and maturation of the BBB since they release sonic hedgehog and retinoic signaling proteins that keep it intact [23]. The perivascular gap is covered by foot-like structures extending from the astrocytes as the BBB grows. At the same time, pericytes are responsible for maintaining the structural integrity of the basal lamina [24].

The BBB is deficient in certain parts (circumventricular regions), such as the area postrema, allowing plasma proteins and viruses to enter the brain.

Transporters Expressed at the BBB

The BBB has two purposes: to protect (or shield) the brain and to transmit chemicals across it. It might enable drugs to enter the brain via one of the following routes: (1) paracellular (between endothelial cells) and (2) transcellular (between cells) transport (involving passage within or through the cell from the luminal to the abluminal surface of the endothelial cell into the parenchyma of the brain). Tight connections between endothelial cells prohibit molecules from passing via the paracellular route, however, molecules may move through the transcellular route depending on their electrochemical gradient (concentration, electrical charge, and lipophilicity). Active transport drives molecules against the concentration gradient through the BBB using adenosine triphosphate (ATP) molecules as a source of energy. Endothelial ion transport (sodium pump, potassium channels, and calcium transporters), endothelial solute carrier-mediated transport (carbohydrate, amino acid, monocarboxylate, hormonal, fatty acid, nucleotide, and organic anion and cation transporters), endothelial active efflux (ATP binding cassettes), and endothelial receptor-mediated trans Endothelial solute carrier-mediated transport (carbohydrate, amino acid, monocarboxylate, hormone, fatty acid, nucleotide, and organic anion and cation transporters); (D) endothelial active efflux (ATP binding cassettes); and (E) endothelial receptor-mediated transport (transferrin, insulin, and lipoprotein transporters). Table 1 expressed novel CNS drugs in trials.

Table 1: Novel CNS drugs in trials.

Drug candidate	Mechanism	Indication	Findings
Sorafenib+everolimus	Tyrosine kinase inhibitor	Brain tumor Glioblastoma Anaplastic glioma	Maximum dose tolerated to be 200 mg twice daily
Sunitinib (high-dose, intermittent)	Tyrosine (multiple) kinase inhibitor	Recurrent GBM	Promising outcomes if intermittent dosage of 300 mg compared to 5 0 mg of previous clinical trial is well tolerated
GnbAC1	Humanized IgG4 mAb targeting retroviral envelope	Relapsing remitting multiple sclerosis	No clear immunoregulatory efect in MS but showed remyelinating potential. Study showed safety and good tolerance of drug

Vandetanib+temozolomide; vandetanib+carboplatin	EGFR and VEGF receptor 2 inhibitor	GBM	Results unclear; well tolerated but efcacy not ascertained, study terminated
ABT-436	Vasopressin 1b receptor antagonist	Alcohol dependence	Greater percent days of abstinence than placebo group
	Peptide receptor antagonist	Acute migraine	Pain freedom within 2 h of 50 and 25 mg; further research needed to determine long-term safety
SAGE-217	Positive allosteric modulator of GABA type A receptor	Major depressive disorder	Administered for 14 days resulted in reduction in depressive symptoms for 15 days but with more adverse events
Rimegepant	Calcitonin gene-related peptide receptor antagonist	Migraine	High percentage of patients free from pain and most bothersome symptoms
Anlotinib With STUPP Regimen	Inhibit both tumor angiogenesis and proliferation	Newly diagnosed and recurrent glioblastoma	
Aducanumab (BIIB037)	Human IgG1 monoclonal antibody against a conformational epitope found on Aβ	Alzheimer's disease	Potentially benefcial being an immune checkpoint inhibitor
1 Selumetinib	Blocks proteins that allow tumor cells grow without stopping	Astrocytoma low-grade glioma	
Selumetinib	Blocks proteins that allow tumor cells grow without stopping	Neurofbromatosis type 1 and symptomatic inoperable plexiform neurofbromas	

Inotuzumab ozogamicin	Monoclonal antibody, linked to anti-cancer calicheamicin	Acute lymphoblastic leukemia CNS leukemia	Improvements in PN-related pain and motor impair- ment, durable tumor shrinkage

Drug Targeting Strategies for the Brain

Drugs are targeted at the brain through a variety of methods. These approaches are divided into two categories: invasive and non-invasive procedures. Invasive procedures such as ultrasonography, osmotic pressure differential, or vasoactive drugs such as bradykinin open or disrupt the neuroprotective barrier between blood and brain. Fig 2 represents Various endogenous transport pathways or transporter systems that are used in the non-invasive technique to transport drugs across the BBB.

Overcoming the BBB with Drug Delivery Methods To get around the BBB, many medication delivery strategies have been explored. Nanoparticles may be utilized to alter an existing medication's drug permeability. Other ways for temporarily disrupting or bypassing the BBB to deliver medications into the brain parenchyma include FUS, CED, intranasal, and intra-arterial administration.

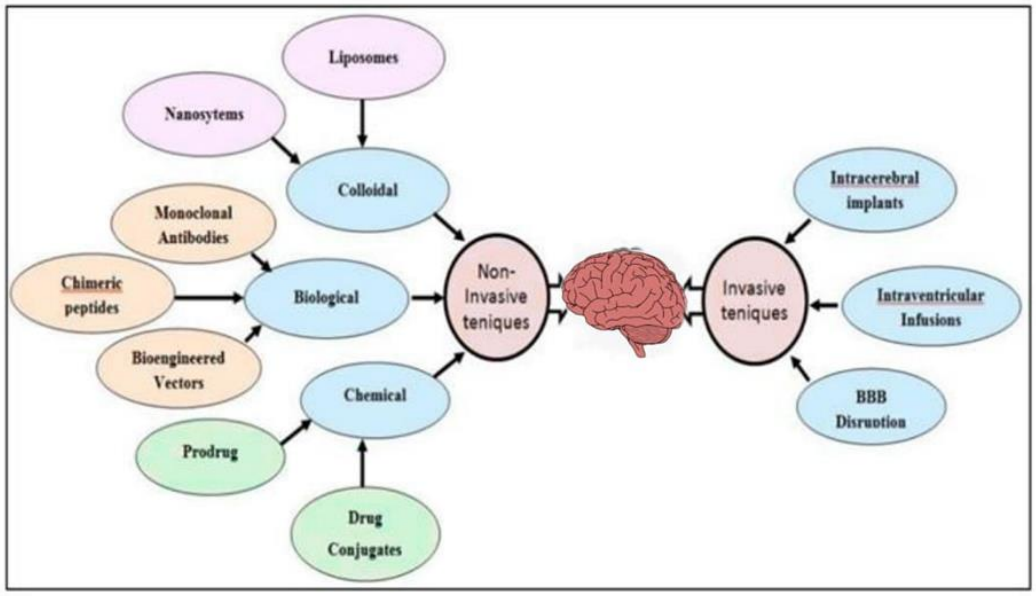

Fig. 2: Various approaches used for delivery of drug to brain.

Drug Penetration in the Brain: Current Methodologies

Different features and kinds of molecules must be understood in order to diagnose and treat a variety of CNS illnesses. Medication delivery methods are now being used by researchers to examine the control of the cellular microenvironment and increase drug delivery efficiency to the brain [25]. Nanocarriers have recently been employed in conjunction with other delivery methods to increase CNS medicine delivery for

disorders including neurodegeneration and brain cancer [26]. Table 2 expresses the novel CNS nanoparticle delivery system for brain targeting.

Table 2: Novel CNS Nanoparticle Delivery Systems.

Sr. No.	Delivery System	Drug/Procedure	Status	Mechanism
1	Viral vector	Preprodynorphin gene	Preclinical	AAV-mediated expression of preprodynorphin in the epileptogenic hippocampus
2	SLN	Coumarin	Preclinical	Borneol-modifed solid lipid nanoparticle loaded with coumarin
3	Polymeric NPs	Elvitegravir	Preclinical	PLGA-EVG NP inhibits efux proteins to optimize CNS delivery
4	Intranasal	RVG29	Preclinical	Targeted PLGA Nanoparticles loaded with rabies virus glycoprotein (RVG29)
5	Targeted NPs	Nevirapine	Preclinical	Polycaprolactone NPs bind to LDL receptors to optimize delivery by RMT
6	Targeted SLN	Zidovudine	Clinical	AZT-SLN receptor specifc RMT across the BBB
7	Non-invasive	MRgFUS	Clinical	Non-invasive BBB disruption at the primary motor cortex using MR-guided
8	Vector	AdV-tk	Phase I	Gene-mediated cytotoxic immunotherapy through local delivery of AdV-tk

Nanoparticles for Brain Delivery

Nanoparticles are small particles made of various packing materials like lipids, polymers, and metals that may be used as a surrogate for more efficient medication delivery. These particles may be made with different compositions to improve their half-life or capacity to target a certain receptor [27]. Nanoparticles have been utilized to treat a variety of cancers with great effectiveness. Endocytosis, receptor-mediated transcytosis, and the increased permeability and retention (EPR) effect are all ways nanoparticles traverse the BBB [28]. The EPR effect makes use of solid tumors' leaky vasculature, allowing nanoparticles to extravasate locally into the tumor. The encapsulated medications are progressively released into the tissue when the nanoparticle is extravasated. Because nanoparticles cannot penetrate normal vasculature in most organs, they are less hazardous to both the peripheral and systemic systems. Nanoparticles have the ability to traverse the permeable BBB, suggesting that they might be used to deliver drugs to brain tumors Nanoparticles, on the other hand, have not been able to achieve therapeutic quantities in tumors in clinical studies [29]. GBM, for example, is defined by intact and disturbed BBB niches. Because of the heterogeneous BBB/ BTB in GBM, medicines are not evenly transported throughout the tumor, leaving certain areas untreated. Furthermore, GBM is characterized by high interstitial pressure and hypoxia, both of which inhibit nanoparticle transit in these locations [30]. As a result, using nanoparticles as a delivery technique for brain cancer therapy has yet to be effective [31]. However, nanoparticles with beneficial features, such as long-term medication release, might be used in tandem with other drug delivery strategies to treat brain cancers.

Ultrasound focusing

Microbubble-mediated focused ultrasound (FUS), also known as sonoporation, is a non-invasive approach for delivering drugs to brain tumors. Microbubbles are forced against the endothelial cell wall by sonic pressure from a transducer and begin to vibrate. The vibration causes stress on the endothelial cell wall, causing the BBB to be temporarily disrupted. Because no neuronal injury, apoptosis, ischemia, or long-term vascular damage has been reported after treatment with ultrasound and microbubbles, the combination is deemed safe. FUS may be combined with traditional chemotherapeutics, antibodies, nanoparticles, and gene-based treatments to provide a wide variety of options.

Magnetic nanoparticles are a new technology for directing therapeutic molecules into brain tumor cells. MNPs are nanoparticles that have magnetic characteristics (Magnetic nanoparticles). These MNPs may form temporary gaps in cell membranes via a process known as magnatoporation, which increases nanoparticle targeting in the brain. These MNPs may also be used for diagnostic or therapeutic purposes.

Liposomes

Liposomes are nano or microcapsules with an aqueous compartment and a lipid bilayer membrane around them. Liposomes vary in size from 0.05 to 0.5 micrometres in diameter [32]. Liposomes were developed in the early 1960s and have since been extensively studied as a medication delivery mechanism for neurological illnesses [33]. Liposomes are non-toxic and non-immunogenic because they are formed of naturally occurring biocompatible substances such as phosphatidylcholine produced from soybean lecithin. Liposomes have been utilized to encapsulate and cotransport both hydrophilic and hydrophobic medicines [34]. Liposomes are being studied for their ability to transport a variety of pharmacologically active substances such as anticancer drugs, vaccinations, chelating agents, and genetic material. Stability was formerly a big issue with liposomes, but thanks to recent advances, this issue may now be solved. Liposomes are classed as tiny unilamellar vesicles, big unilamellar vesicles, or multilamellar vesicles based on the number of bilayers present [35]. Drugs like doxorubicin and daunorubicin have been cleared for clinical studies in liposome-based formulations. Liposomes are used to synthesize small hydrophobic compounds including rivastigmine, tacrine, resveratrol, donepezil, and curcumin. The fundamental issue with these medications is their low water solubility, which may be solved by synthesizing them in liposomal form for neurodegenerative disease therapy [36]. Liposomes also eliminate a number of drawbacks associated with traditional formulations, including limited bioavailability and non-specificity [37]. Fig. 3 represents the various transport pathway of liposomes toward BBB Carrier-mediated transport, passive transcellular diffusion, transferrin receptor, insulin receptor-mediated transcytosis, absorptive-mediated transcytosis, cell-mediated transcytosis, and efflux pumps are some of the methods liposomes enable drugs to cross the BBB [38]. The major transfer mechanism for the liposome delivery technology is receptor-mediated transcytosis. Liposomes may easily traverse the BBB and deliver therapeutic medicines to the CNS through transferrin (TfR) or insulin receptors (IR) [39]. Liposomes may also be linked to glial fibrillary acidic protein (GFAP) monoclonal antibodies to traverse the BBB. Recent research used a liposomal nanohybrid cerasome synthesized from polysorbate 80 as a P-gp inhibitor to improve curcumin BBB permeability in the treatment of Parkinson's disease, with promising results [40]. To improve therapeutic effectiveness, ferromagnetic liposome-based drug delivery systems have been developed in recent years. Fe3O4 aided liposomes may be targeted to the spot with enhanced pharmacokinetic characteristics using an external magnetic field. The Fe3O4-modified nimodipine liposomes were discovered to penetrate the BBB effectively.

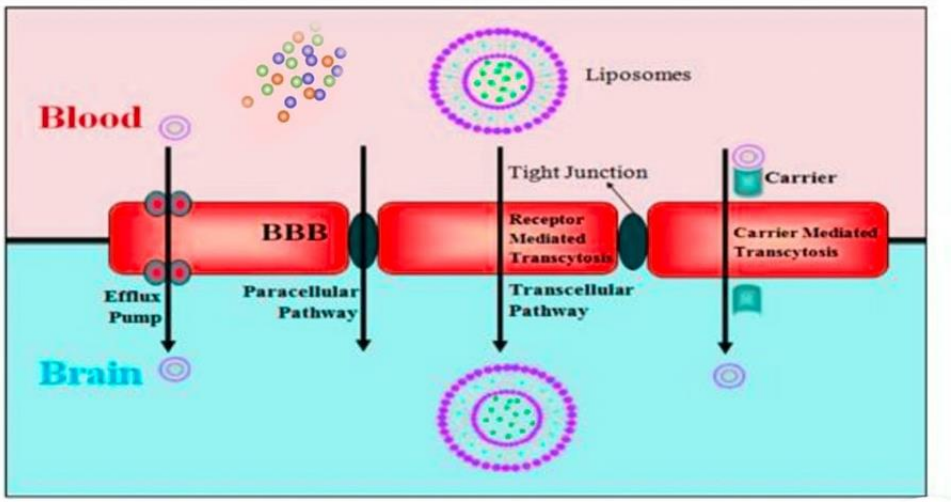

Fig. 3: Various transport pathways of liposome through BBB.

Dendrimers

Dendrimers are nanoscale macromolecules with a hyperbranched spherical shape that are commonly used in medication delivery. Dendrimers, unlike typical polymeric nanovesicles, are monodisperse and have well-defined chemical structures. Dendrimers also have the benefit of being able to load medicinal medicines through covalent conjugation or electrostatic adsorption due to their unique structure [41]. Dendrimers are made up of three parts: a central core made up of a single atom or group of atoms, building units called generations linked to the central core, and functional groups located on the surface (Fig. 4).

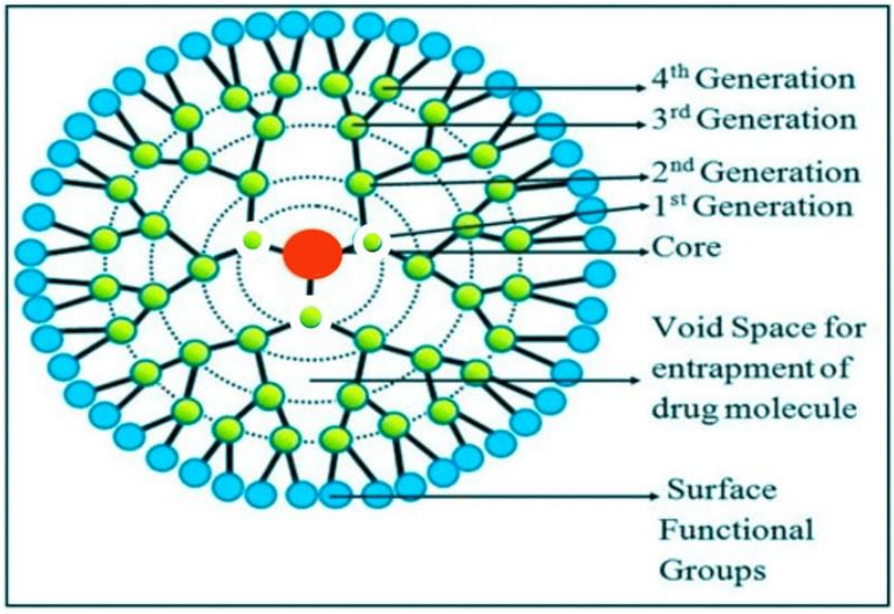

Fig. 4: Structure and generations of dendrimers.

The majority of dendrimers are made utilizing two methods. The first way, known as the divergent method, involves building dendrimers from the core to the perimeter, whereas the second method, known as the convergent method, involves building dendrimers from the periphery to the centre [42]. The outer groups may have positive, negative, or neutral charges, which is crucial for utilising dendrimers as a preferred drug delivery transporter [43]. Drug molecules may be physically enclosed in the interior chambers of dendrimer molecules or chemically attached to the surface functional groups to target drugs into the brain utilising dendrimers. Drug molecules may be targeted into the brain via a variety of ways. The following are a few of them. Transferrin receptor targeting may be used to target polyamidoamide [PAMAM] dendrimers into the brain. LRP1 and LRP2 [low density lipoprotein receptor-related proteins] are multifunctional forager receptors found on the BBB. They may attach to a variety of substances and cause them to cross the BBB. Dendrimers have the ability to connect to these receptors and traverse the BBB. Another way to use dendrimers to target drugs is via the glucose transporter system. The glucose transporter system is used to get glucose into the brain. With the use of dendrimers, this transporter system may be used to target drugs into the brain [44].

Prodrug Strategy

The chemical moiety that undergoes biotransformation before displaying therapeutic action is known as a prodrug. In 1958, the word "prodrug" was coined. Another name for the prodrug is a pro agent. A prodrug is a bio-reversible derivative of a drug molecule and pro-moiety that undergoes a chemical or enzymatic transformation into an active form within the body before exhibiting pharmacological action (Fig. 5).

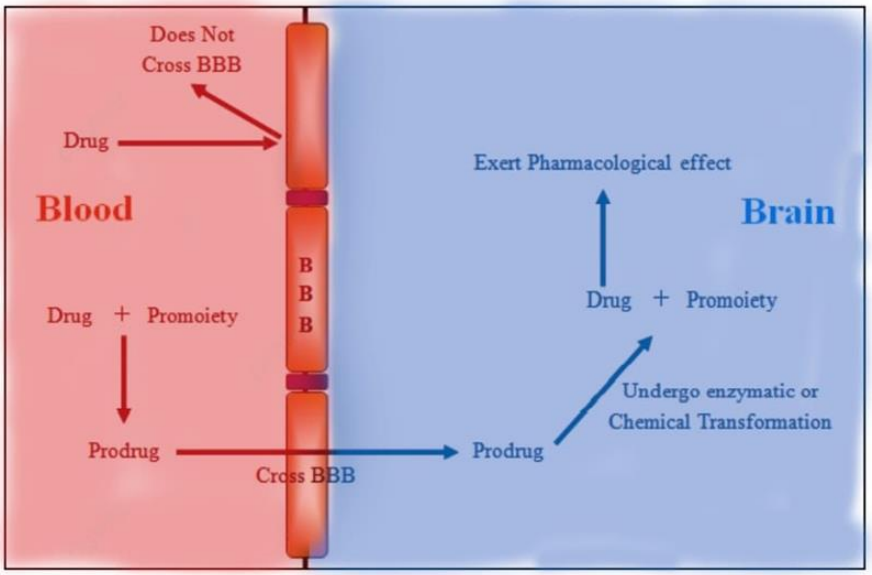

Fig. 5: Illustration of Prodrug concept.

Innovative Techniques

The difficult topic of efficient brain delivery has sparked intense scientific interest, resulting in the invention and patenting of several innovative approaches. Researchers have disclosed the use of iontophoresis as an adjuvant for CNS medication delivery in this series. The active delivery of ionized compounds into tissues through an electric current is known as iontophoresis. The parent US patent technique and apparatus for delivering a biologically active substance directly to the CNS by iontophoresis and/or phonophoresis, bypassing the BBB, is known as trans-nasal iontophoretic delivery [44].

Molecular Trojan Horses

Trojan horses are endogenous ligands for certain BBB receptors that have the ability to transport medicines into the brain. The vasoactive intestinal polypeptide (VIP) regulates cerebral blood flow; however, in vivo investigations revealed negligible neuropharmacological impact due to limited peptide transport to the brain, which is due to the existence of the BBB.

CONCLUSION:

Is it possible to go around the BBB and give contemporary treatment a chance? So far, we've looked at a few medication delivery methods that have been created to get around the BBB. However, in patients with primary brain tumours, most approaches have not resulted in a meaningful improvement in survival. The lack of understanding of the BBB/BTB and vascular in both adult and juvenile brain tumours is one of the key reasons why medication delivery strategies have failed. We looked at a number of BBB diseases, and practically all of them have gaps in their knowledge of the BBB pathology of specific cancers. The necessity of understanding the characteristics of the BBB to increase survival has been shown by paediatric medulloblastoma. When compared to the other subtypes, the WNT subtype of medulloblastoma has a dysfunctional and high vascular density, making it curable with standard therapy. Understanding the features and difficulties of the BBB/BTB may help with medication delivery strategy optimization. Because FUS necessitates the systemic delivery of microbubbles and medicines, highly vascularized tumours may benefit more from it. Furthermore, FUS has the ability to decrease efflux transporters, which might benefit drug accumulation and retention in the brain parenchyma. CED, on the other hand, is best suited for tumours with modest vascular density and an intact BBB to avoid drug 'leakage' from the tumour site. By combining methods like FUS with nanoparticles or immunotherapy, a multimodal strategy to treating brain cancers may be required. To further tailor chemotherapy administration, we encourage doctors, researchers, and biotech businesses to collaborate to define BBB/BTB from patient samples. It is not an easy task to target a medicine to the brain. The Blood Brain Barrier's security system makes it harder to transfer drugs into the brain. However, medication transport over the BBB into the brain is required for the treatment of numerous neurological illnesses such as Alzheimer's disease, Parkinson's disease, and brain cancers. It is possible to

traverse the BBB utilizing endogenous transporter mechanisms, receptor-mediated transport, or efflux pump-mediated transport.

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