REVIEW ARTICLE

Brain Drug Delivery System: A Novel Review

P. Anitha[1], G. Venkata Sowmyasree[1], Prasanthi Samathoti[2], C. Ronald Darwin[3], P. M. M. Naga Lakshmi Varma[4], A. V. S. Himabindu[4], A. V. S. Madhu Latha[5], S. Sravana Kumari[6], S. Ashok[7], V. Sarovar Reddy[1]*

[1]Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [2]Department of Pharmaceutics, Mohan Babu University (Erstwhile Sree Vidyanikethan College of Pharmacy, Tirupati, Andhra Pradesh, India, [3]Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, India, [4]Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences For Women, Vijayawada, Andhra Pradesh, India, [5]Department of Pharmaceutics, Siddhartha Institute of Pharmaceutical sciences, Jonnalagadda, Palnadu District, Andhra Pradesh, India, [6]Deparatment of Pharmacy Practice, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [7]Department of Pharmaceutical Analysis, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India

Abstract

In the living world, 1.5 billion of people have been suffering from either one or another brain disease. The most probably causing diseases/disorders related to the function of the brain were autoimmune encephalitis, autoimmune epilepsy, Hashimoto's encephalopathy, Alzheimer's disease (AD), and Wilson's disease. As the brain's extracellular matrix contributes to the poorly distributed delivery of locally administered medications and the blood-brain barrier functions as an impenetrable barrier for systemically injected treatments, drug targeting in the brain is one of the most difficult problems in pharmaceutical research. General strategies that can enhance medication delivery to the brain are very desirable for the treatment of several disorders affecting the central nervous system (CNS). When medications are given close to their optimal sites of action, they are both less hazardous and more effective. Several methods or novel approaches have been developed through various investigations to target the drug to reach the affected area in the brain. The BBB is the most hurdles for the active ingredients to exhibit its function so numerous approaches such as Nanoparticles, Lipoplexes, Scaffolds, Dendrimers, Polyanhydride, and Receptor-mediated transport (RMT) have been developed for improving drug action.

Key words: Blood-brain barrier, central nervous system, scaffolds, Alzheimer's disease, convection-enhanced drug delivery

INTRODUCTION

The brain is a sensitive organ that nature has skillfully shielded. Because the blood-brain barrier only allows certain molecules to get through, drug delivery into the brain has proven to be challenging. The blood-brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB) are the two primary barrier systems that protect the brain from potentially harmful substances. Regretfully, the same defenses against invasive chemicals can also work against therapeutic attempts. Technology has made significant technological advancements possible in recent decades, including very accurate and efficient medicine delivery into the brain. Effective brain delivery is a difficult field that has sparked intense scientific research, leading to the invention and patenting of numerous cutting-edge techniques. We provide a summary of significant recent developments in brain-targeted medication delivery in this study. The BBB and BCF, which guard the central nervous system (CNS), regulate brain homeostasis by limiting

Address for correspondence:
Dr. V. Sarovar Reddy, Department of Pharmaceutics, Annamacharya College of Pharmacy, New Boyanapalli, Rajampet - 516 126, Andhra Pradesh, India.
Phone: 9493035229.
E-mail: sarovar.ancp@gmail.com

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the entry of chemicals into the brain. Barriers prevent blood-borne substances from entering brain cells and make it easier for nutrients needed for a healthy metabolism to enter brain cells. Certain medications, both large and small, are unable to pass through the blood-brain barrier (BBB) due to this control of brain homeostasis. It is estimated that nearly all large molecular-weight drugs (primarily peptides and proteins) and over 98% of small molecular-weight drugs developed for CNS pathologies are unable to cross the BBB. Therefore, finding new ways to effectively deliver drugs and bio macromolecules to the CNS is crucial for treating neurodegenerative disorders such as epilepsy and Alzheimer's disease.[1]

ANATOMY OF BRAIN

The brain, which is composed of a sizable mass of nerve cells that are covered by the skull, serves as the command center of the Central Nervous System (CNS).[2-4] The cerebellum, brainstem, and cerebrum are its three main components. It manages the body's intellectual functions, including organizing, integrating, and processing the data gathered from the sense organs. It is a jelly-like mass of tissue with 86 billion nerve cells inside that weighs roughly 1.4 kg.[5-8] The brainstem, which on the other end links to the spinal cord, is related to the cerebrum. Several brain regions, including the thalamus, pineal gland, hypothalamus, pituitary gland, amygdala, and hippocampus, are located beneath the cerebral cortex. Each cerebral hemisphere's cross-section reveals a ventricular cavity, which is the site of production and circulation of the cerebrospinal fluid. The septum pellucid, a membrane that divides the lateral ventricles, is located underneath the corpus callosum.[9,10] The majority of the human brain is located in the cerebrum. It comprises two cerebral hemispheres, each accounting for two thirds of the brain's total weight. Language and speech are controlled by one functionally dominant hemisphere. Interpretation of spatial and visual data is done by the other hemisphere.

The corpus callosum is a bundle of nerve fibers that connects the left and right hemispheres of the human brain. The frontal, temporal, parietal, and occipital lobes are the four lobes that make up each hemisphere.[11-18] Cognitive skills, such as emotional expression, problem-solving, memory, language, judgment, and sexual behavior are all under the voluntary control of the frontal lobe.[15] Controlling primary auditory sensations, such as hearing, the temporal lobe houses the primary auditory cortex, which interprets sensory data from secondary areas and the ears and converts it into meaningful language. They are communicated through words and speech.[16] Information about touch, taste, movement, and warmth is processed by the parietal lobe.[14] Vision is mostly controlled by the occipital lobe.[17]

Neurons are the brain's actual cells, and glial cells are the non-neuron cells that support them. An adult human brain's average size is about 86 billion neurons. The Latin term for "glue" is "glia".[19] There are three primary glial cell types are oligodendrocytes, which aid in axon insulation and the appropriate transmission of electrical signals across great distances at a high rate of speed; Microglia, also referred to as CNS immune cells, are mobile brain structures that communicate with one another continuously; Astrocytes: These cells, which resemble stars, sustain the BBB supply the neurons with nourishment, health nerve tissue, and enable neurotransmission.[20-22]

A system or formulation technique that aids in delivering pharmaceutical chemicals into the body to provide the intended therapeutic effect is referred to as "drug delivery." to interact more effectively with the infected tissues and exhibit the intended therapeutic effect.[23]

Since brain-related illnesses, such as brain cancer and abnormalities of the CNS are among the most important, debilitating, and trending illnesses in the world.[24]

However, research has looked into the use of macromolecules (proteins) and small molecules (molecules) as potent pharmacological agents to treat brain diseases.[25] It has been discovered that medications with a lipophilic molecular weight of less than 40 Da can pass right through the BBB. Drug development for brain illnesses has slowed down as a result of the BBB's obstruction, which has prevented 95% of medications from entering the brain.[26] Our major goals are to reexamine the fundamental ideas behind brain medication delivery, identify novel approaches for doing so, and examine the most current advancements in brain-targeted drug delivery systems over the previous 5 years.

The ideal conditions for a chemical to get through the BBB are thought to be. (1) A union should be formed for Compound. (2) Approximately, logP must equal 2. (3) Its molecular weight ought to be under 400 Da. (4) The total number of hydrogen bonds should not exceed 8–10. (5) Only 2% of tiny molecular weight drugs are predicted to pass the BBB.[27]

BARRIERS TO CNS DRUG DELIVERY

There are several obstacles that prevent medications from being administered systemically to the CNS, which helps to explain why many CNS disorders remain untreated despite this fact.[28-41]

APPROACHES FOR DELIVERY OF DRUGS TARGETED TO THE BRAIN

Many medication delivery techniques have been devised to get beyond the many obstacles preventing potential therapeutic medicines from being delivered to the CNS.

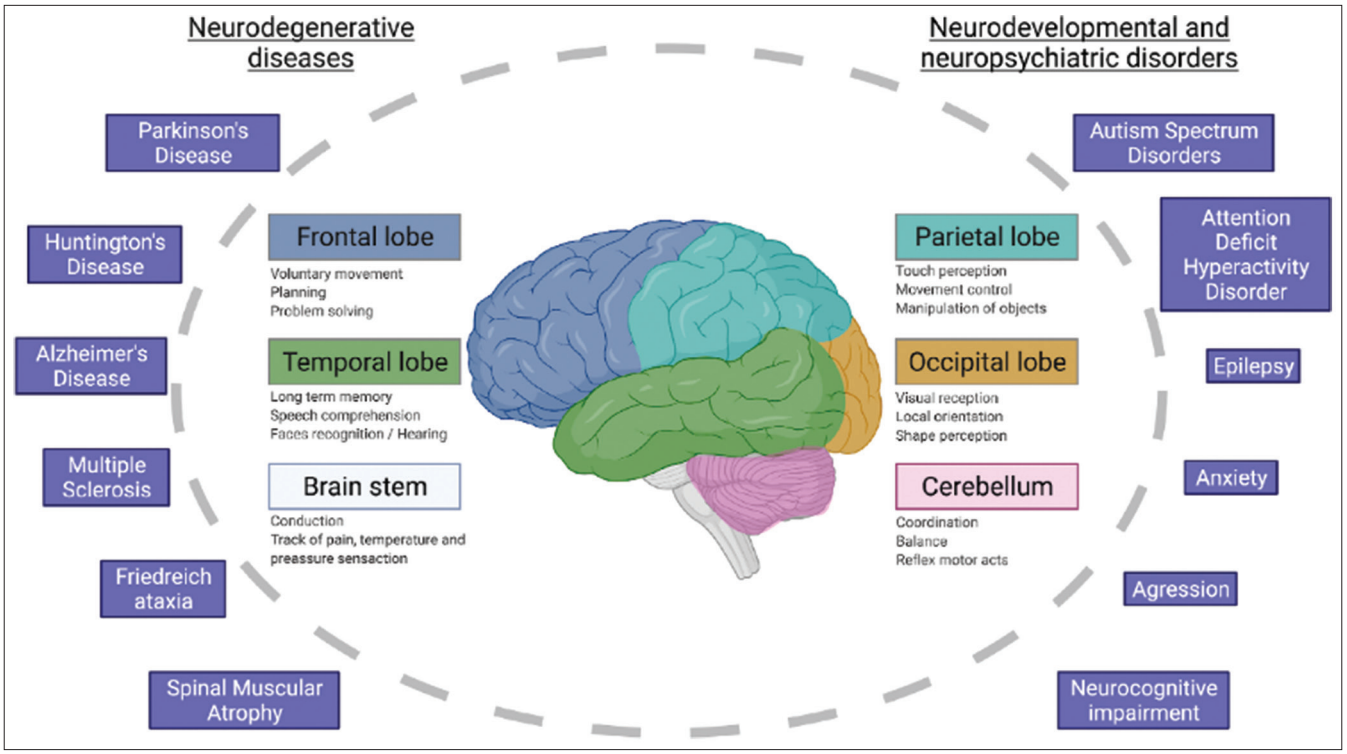

Figure 1: Neurodegenerative, Neurodevelopment and Neuropsychiatrric disorders

These tactics typically fit into one or more of the following classifications: non-invasive, intrusive, or other techniques. The picture below depicts the CNS drug delivery tree that includes all of the potential approaches.

BRAIN DISORDERS

The entire body is impacted by any abnormalities, illnesses, or dysfunctions that affect the brain. The brain is prone to tissue infection, neurons, and neuronal disorders. Trauma (a mental illness) and strokes (an unintentional or environmental blood supply cutoff) can both result in damage. Brain cell degeneration happens as a result of brain damage.[42,43] It is dependent on numerous internal and external factors. While neurotoxicity refers to chemically generated neuronal damage, trauma-related brain damage is caused by external forces or psychologically unstable conditions.[42] Neuropsychiatric disorders and neurodegenerative diseases are the two main categories into which broadly speaking human brain problems in Figure 1. Both conditions are difficult to comprehend and incurable, but they can be treated or their symptoms can be suppressed with the use of medications, surgeries, and physical therapy in Table 1.

Novel method-recent advances in brain targeting drug delivery

1. Dendrimers
2. Scaffolds
3. Lipoplexes and Polyplexes
4. Polyanhydrides

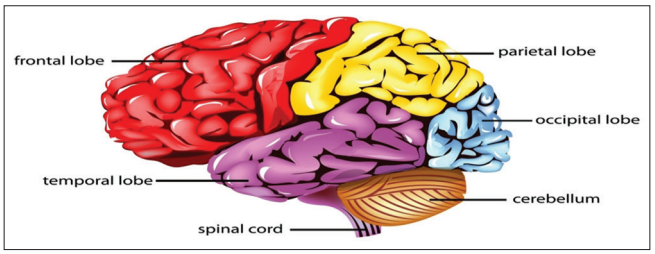

Figure 2: Parts of the human brain

5. Modified nanoparticles
   - Multifunctional nanoparticles
   - Magnetic nanoparticles.
6. Receptor-mediated transport (RMT).
   - Monoclonal antibody (MAb) molecular Trojan horses (MTH)
   - Trojan horse liposomes for CNS gene therapy
   - *In vivo* brain imaging of gene expression
7. Transporter-independent mechanisms to circumvent the BBB.
   - Convection-enhanced drug delivery (CED)
   - Bradykinin receptor-mediated BBB opening
   - Ultrasound-mediated BBB opening.[45]

Novel methods of drug delivery was shown in Figures 2-13.

Dendrimers

Dendrimers are branching polymers that resemble a tree's structure. When a dendrimer is sufficiently stretched, it frequently takes on a spheroidal three-dimensional form in

Table 1: Types of human brain diseases/disorders with their symptoms and treatments

Serial number	Type of diseases/ disorders	Parts of the brain affected	Symptom(s)	Treatment(s)
		Category - Autoimmune diseases[44]		
1	Autoimmune encephalitis	Brain cells	Impaired speech, balance, or vision psychosis; hostility; inappropriate sexual conduct; panic attacks	Excision of the tumor and intravenous immune suppressive medication
2	Autoimmune epilepsy	Brain cells	Recurrent seizures that are out of control	Combined with intravenous immunoglobulin
3	Central nervous system vacuities	Inflammation of blood vessels in the Brain	Headaches, seizures, brief ischemia episodes, disorientation, weakness, visual issues, convulsions, and encephalopathy	High-dose steroids combined with cyclophosphamide, such as prednisone
4	Hashimoto's encephalopathy	Lymphocytic vacuities of venules and veins in the brain stem	Aggression, delusional conduct, personality shifts, focus, and memory issues, jerks in the muscles, confusion, headaches, lack of coordination, psychosis	Corticosteroids
5	Optic neuritis	Fatty coating adoptic nerve is Inflamed	Loss of color vision and a hazy or fuzzy vision occur	Vitamin B12 and intravenous immune globulin
6	ASD	Hippocampus amygdala, lobes of the cerebrum ventricles	Adoption of odd speech patterns, speaking in a robotic tone, avoiding eye contact, developing speech skills later	Adoption of odd speech patterns, Therapies for behavior and communication, occupational therapy, sensory therapy, speech therapy
		Category - Dementia[44]		
1	Fronto -temporal dementia	Degeneration of the temporal and frontal lobes	Incapacity to focus or plan; frequent, rapid mood swings; socially inappropriate behavior; lack of restraint	Medications that are antipsychotic and antidepressant
2	Dementia with Lewy bodies	Clumps of a protein in Cortex	Movement tissues, unbalance, hallucinations, and disturbed sleep	Carbidopa, levodopa, and cholinesterase inhibitors
3	Vascular dementia	Blocking of Blood vessels	Short-term memory issues, inappropriate sobbing and laughing, difficulty focusing, making plans, handling money	Managing high blood pressure with medicine, diet, and exercise
4	AD	Destroy neurons and their connections in parts of the brain	Reduced energy, diminished enthusiasm for job and social interactions, memory loss resulting in the forgetting of recent discussions and events	Tacrine, Rivastigmine, and Donepezil

(*Contd*...)

Table 1: (*Continued*)

Serial number	Type of diseases/ disorders	Parts of the brain affected	Symptom(s)	Treatment(s)
		Category - Brain infections[44]		
1	Meningitis	Inflammation of the meninges, brain and spinal cord	Reduced appetite, agitation, fatigue, fever, sensitivity to strong light, drowsiness nausea, vomiting, disorientation, and confusion	Steroids, any swelling around the brain, oxygen through a face mask if breathing difficult intravenous fluids to avoid dehydration
2	Encephalitis	Temporal lobe, frontal lobe	Headache, fever, pains in muscles or joints, weariness or weakness, disorientation, agitation, seizures, loss of sensation	Corticosteroids, ganciclovir, and acyclovir
3	Brain abscess	Fungal and viral infection in the brain	Variations in mental processes, including heightened disorientation, and agitation; speech; sensation; reduced mobility	Antibiotics as well as surgery
		Category - Movement disorders[44]		
1	Ataxia	Cerebellum	Unsteady gait and a propensity to stumble, trouble with fine motor like involuntary back and forth eye movements	Physical and mental exercise, occupational treatment, and speech and language therapy
2	Dystonia and Cervical dystonia	Basal ganglia	Dragging leg, cramping of the foot, involuntary tugging of the neck, and uncontrollable blinking	Procyclidine, hydrochloride, baclofen, lorazepam, diazepam, and clonazepam
3	HD	Nerve cells and basal ganglia	Uncontrollably jerking or writhing; muscle issues, such as contracture or stiffness; sluggish poor posture, balance, and walking; trouble speaking or eating	Antipsychotic medications such as levetiracetam and clonazepam
4	PD	Nerve cells, basal ganglia, and substantia nigra	Tremor, trembling hand or fingers, delayed movement, tight muscles, decreased posture and balance, loss of instinctive movements, speech alterations	Levodopa, dopamine agonists, MAO B inhibitors, catechol anticholinergic, amantadine, carbidopa levodopa infusion
5	RLS	Cingulate cortex and cerebellum	Feelings following repose, symptoms getting worse tight and in the evening, and periodic twitching of the legs	Muscle relaxants, Rotigotine, Pramipexole, Gabapentin, Pregabalin, and Hydrocodone
6	Wilson's disease	Brain and spinal cord	Fatigue; lack of appetite; pain in the abdomen; yellowing of skin and white eyes	Trientine, Penicillamine, T-Zinc acetate, and surgery

(*Contd*...)

Table 1: (*Continued*)

Serial number	Type of diseases/ disorders	Parts of the brain affected	Symptom(s)	Treatment(s)
		Category - Neuromuscular diseases[44]		
1	ALS	Degeneration of nerve cells in the spinal cord and brain	Twitching/cramping of muscles, loss of motor control in the hands and arms, impairment and legs, tripping and falling, dropping items	Nutritional, respiratory, speech, occupational, and physical therapies
2	Charcot-Marie-Tooth disease	Axon	The following symptoms may be present: numbness, tingling, burning	Orthopedic devices, physical and occupational therapy
3	Multiple sclerosis	Brain, spinal cord, and nerve cells	Reddish green color distortion, double/blurred vision, loss of vision due to optic nerve swelling, and difficulty walking	Workout regimens that increase muscle control, endurance, and strength
4	Muscular dystrophy	Absence of protein dystrophin in neurons	Atrophy, or progressive muscle weakening and wasting, is characterized by a waddling gait	Exercise, physical treatment, and prednisone
5	Myasthenia gravis	Neurons	Issues with vision, ptosis and diplopia, weariness, and muscle weakness	Anticholinesterase medications, immune inhibitors
6	Peripheral neuropathy	Nerves in the brain and brain stem	Gradual onset of burning, throbbing, numbness; lack of coordination weakening of the muscles, paralysis	To prevent seizures, topical therapy antidepressants, and transcutaneous electrical nerve stimulation
		Category - Seizure disorders[44]		
1	Tonic-clonic seizures or Grand mal seizure	Cerebellum, basal ganglia	Loss of bladder and bowel control, confusion, exhaustion, and a strong headache and in responsiveness seizures	Medications such as lamotrigine, phenytoin, carbamazepine, topiramate, phenobarbital
2	Atonic seizures	Alterations in brain function	Rapid lack of strength in their muscles, go limp and fall to the ground	Zarontin with Depakene
3	Myoclonic seizures	Temporal lobe	Sudden increases in muscle tone, sudden spasm, occasionally and falling asleep	Antiseizure drugs, nerve stimulation, or surgery
4	Absence seizures/Petit mal seizures	Thalamus	Lip smacking, eyelid flutters, motions, finger rubbing, and little movements	Lamotrigine, ethosuximide, and valproic acid
		Category - Stroke diseases[44]		
1	Trauma	Alterations in brain function	Momentary unconsciousness, mental confusion, headache, nausea, exhaustion	Emergency attention, prescription drugs, surgery

(*Contd*...)

Table 1: (*Continued*)

Serial number	Type of diseases/ disorders	Parts of the brain affected	Symptom(s)	Treatment(s)
2	Tumors	Brain cells	Headache, nausea, vomiting, visual issues progressive paralysis of an arm or limb, trouble speaking	Surgery targeted drug therapy, radiation therapy, chemotherapy, scar-free brain surgery
		Category - Mental disorders[44]		
1	Anxiety disorders, including panic disorder and phobia	Amygdala	Fatigue, difficulty falling asleep, twitching or tense muscles, trembling, nausea, diarrhea, and irritability	Benzodiazepines, buspirone, and antidepressants are utilized in psychotherapy
2	Post-traumatic stress disorder	Cingulate cortex and frontal gyrus	Negative ideas, issues with remembering, inability to sustain intimate relationships, and emotional numbness	Eye movement desensitization, Psychotherapy, antidepressants, and anxiety reducer
3	Psychotic disorders, including schizophrenia	Medial frontal lobe	Hallucinations, unpleasant symptoms, sleep difficulties, depression, lack of motivation, and disorganized thinking	Aripiprazole, asenapine, brexpiprazole, paliperidone, and long-acting injectable antipsychotics
4	Eating disorders	Brain cells	Unusually low body weight, severe anxiety about gaining weight, and frequent	Cognitive behavioral therapy, antidepressants, anxiety-reducing drugs
5	Personality disorders	Amygdala, prefrontal cortex	Aggression toward people and animals, stealing, being constantly irresponsible	Psychoanalysis

ASD: Autism spectrum disorder, ALS: Amyotrophic lateral sclerosis, PD: Parkinson's disease, RLS: Restless legs syndrome, HD: Huntington's disease, AD: Alzheimer's disease

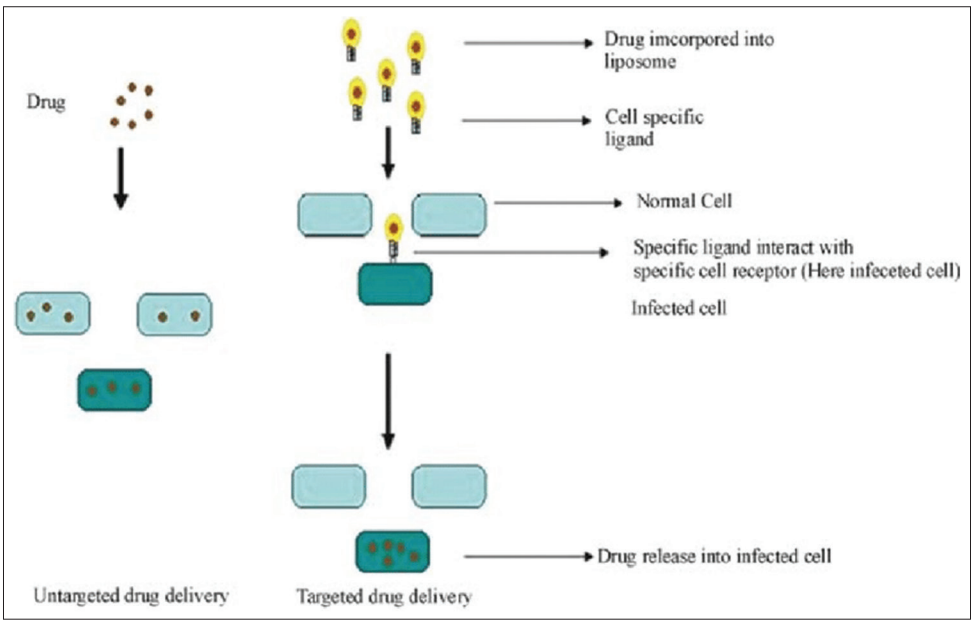

Figure 3: Drug targeting technology

water. Dendrimers are normally symmetric around the core. Their structure exhibits a central core that possesses at least two identical chemical functions. In the brains of newborn rabbits with cerebral palsy, Kannametal demonstrated that systemically injected polyamidoamine dendrimers localize in activated microglia and astrocytes, offering potential clinical application in the treatment of neuro-inflammatory illnesses in humans.[46]

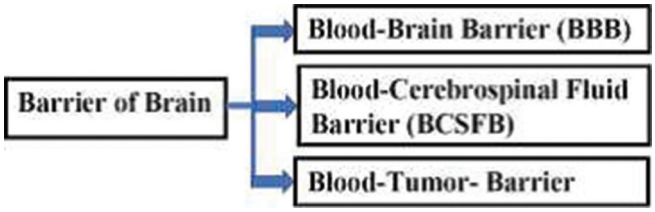

Figure 4: Barriers in brain targeted drug delivery system

Scaffolds

Implantable scaffolds can be utilized for medication delivery to treat neurological diseases, such as Parkinson's and Alzheimer's disease, as well as a number of conditions related to brain injury and diseases.

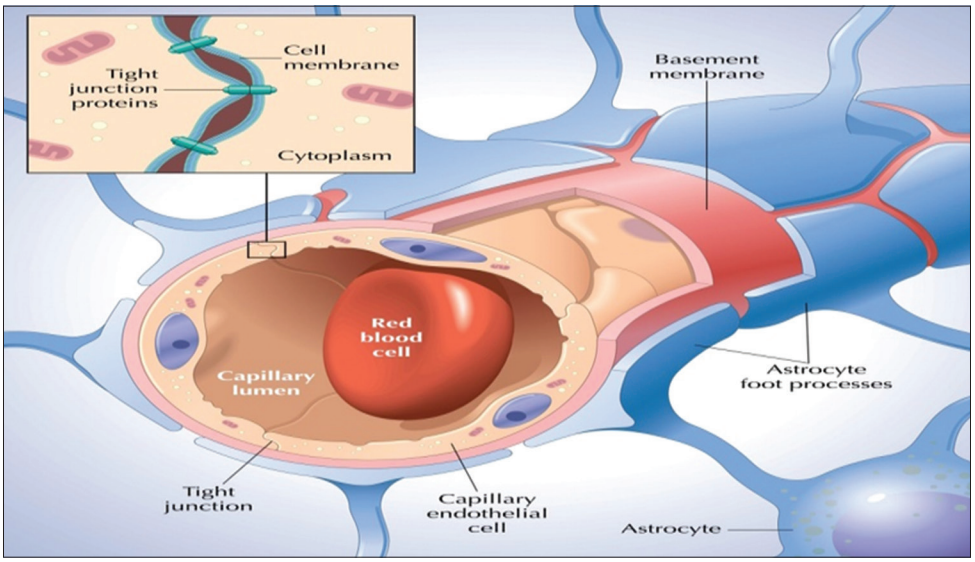

Figure 5: Blood-brain barrier

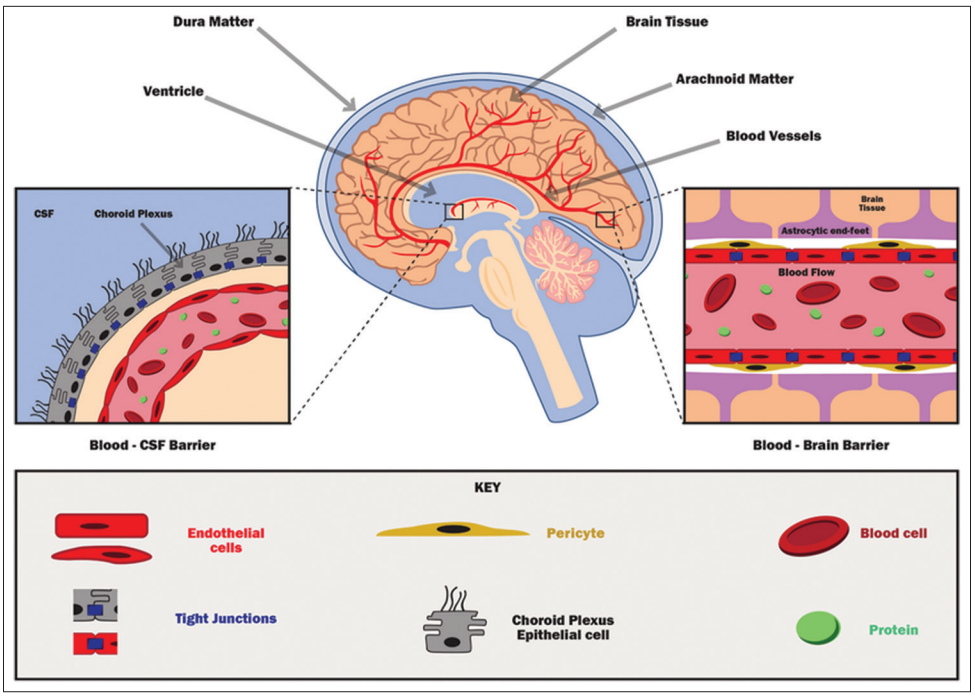

Figure 6: Blood cerebrospinal fluid barrier (BCSFB)

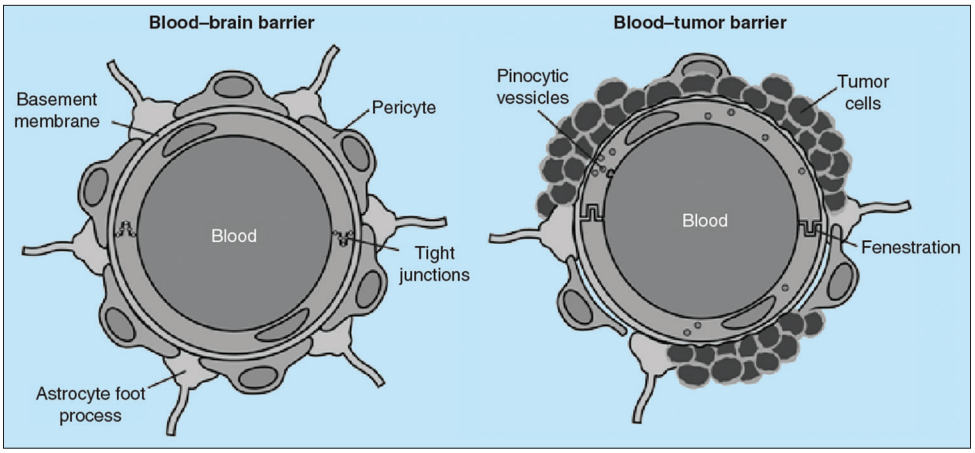

Figure 7: Blood-tumor barrier

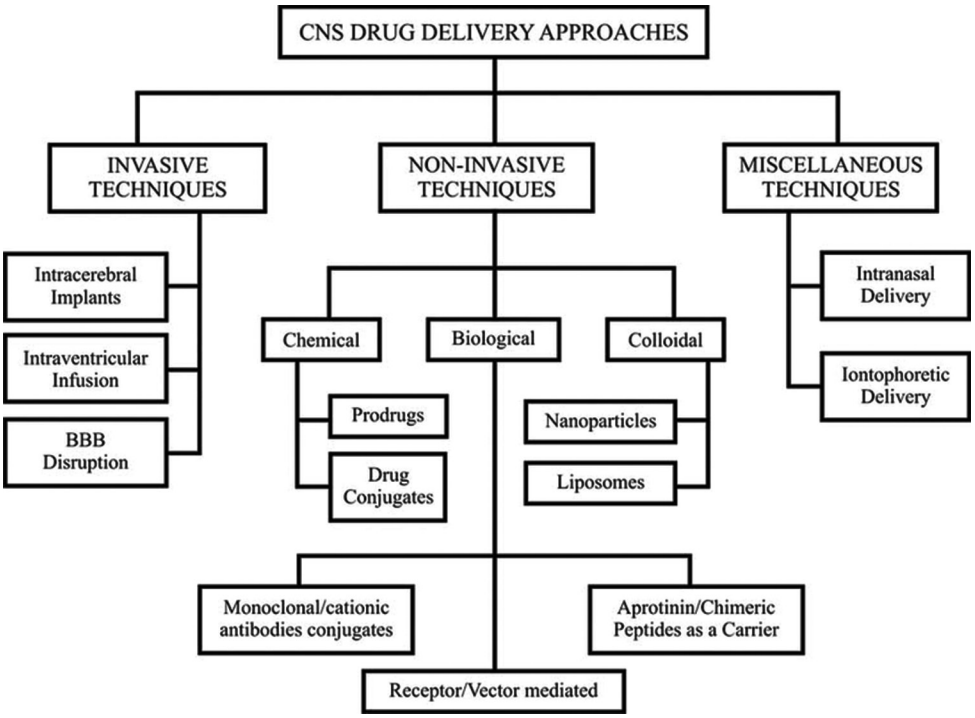

Figure 8: CNS drug delivery approaches

Scaffolds for brain drug delivery

Effectiveness of poly PHPMA and PHEMA scaffolds with glucosamine or N-acetyl glucosamine groups when placed in a fimbria-fornix lesion cavity between the hippocampal and septal regions. It was discovered that compared to PHPMA, PHEMA scaffolds exhibited noticeably reduced connective tissue invasion.[45]

Lipoplxes and polyplexes

The DNA needs to be shielded from harm and given easier access into the cell to enhance the transport of the new DNA into the cell. For this, lipoplexes and polyplexes are utilized. Both are capable of shielding the DNA during transfection against unintended deterioration. Lipids can coat plasmid DNA in a structured form resembling a liposome or micelle. A lipoplex is created when DNA forms a compound with the ordered structure. Lipids come in three different varieties: Anionic both cationic and Neutral.

Originally, lipoplexes for synthetic vectors were made from neutral and anionic lipids. The lipoplexes exhibit minimal toxicity, can be tailored to target specific tissues, and are compatible with bodily fluids. The main drawback is that producing them takes a lot of effort and complexity.[45]

Polyanhydrides in brain tumor

Brain tumor about 80% of adult primary brain tumors are glioblastoma multiform (GBM), which are often located in the cerebral hemispheres. Large molecular architectures,

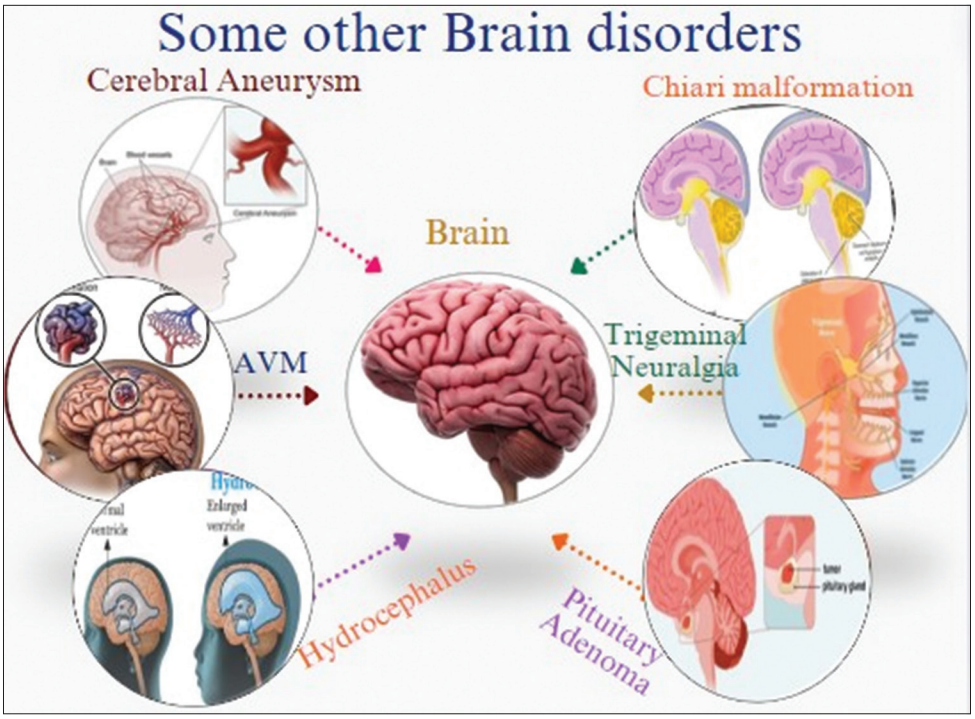

Figure 9: Other brain disorders

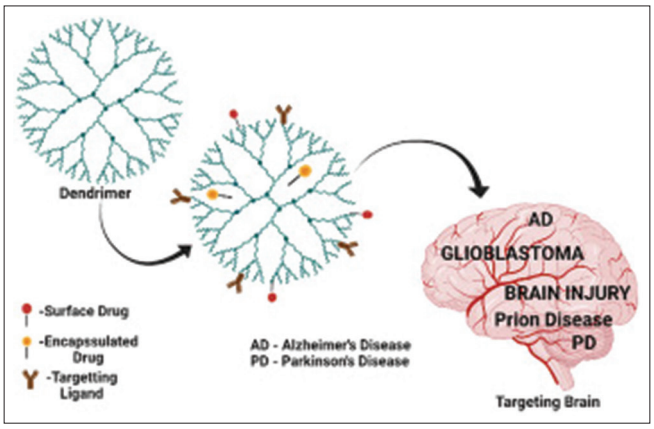

Figure 10: Dendrimers

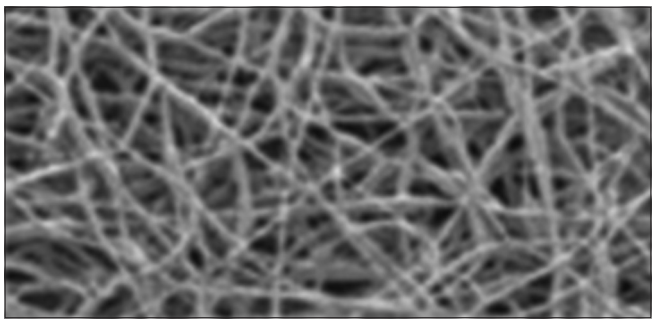

Figure 11: Scaffold

ionic charges, or hydrophilicity make many anti-cancer medications unable to penetrate the BBB. As a result, intolerably high systemic levels are needed to reach the therapeutic doses within the CNS. One of the easiest methods for direct localized distribution is the use of polyanhydrides.

- FDA approved Gloadel wafers in 1996. These are among the most effective polyanhydride delivery systems and are offered for sale. They are composed of 20:80 Poly (CarboxyPhenoxy) Propane: Sebacic Acid.[45]

Modified nanoparticles

The use of nanoparticles as a delivery vector for drugs to the brain offers the following benefits:

- Superb engineer ability, Non-toxicity.
- Targeted nanoparticles can deliver significant volumes of therapeutic or imaging agents with controlled loading and release of active agents (drugs/contrast agents).
- Enhanced surface features (targeting and/or hydrophilic coating) in nanoparticles hence increasing the effectiveness of current cancer treatments and imaging methods.
- The following is most likely the precise method of nanoparticle transfer into the brain: The processes of receptor-mediated endocytosis, phagocytosis, and passive leaking across BBB abnormalities.

Types of nanoparticles

- Multifunctional nanoparticles: Multifunctional nanoparticles are 20-200 nm diameter nanoparticles. These are also called as Probes
- Magnetic nanoparticles for MRI
  Typically, short-lived Gadolinium-based contrast agents are used during CNS MRIs.

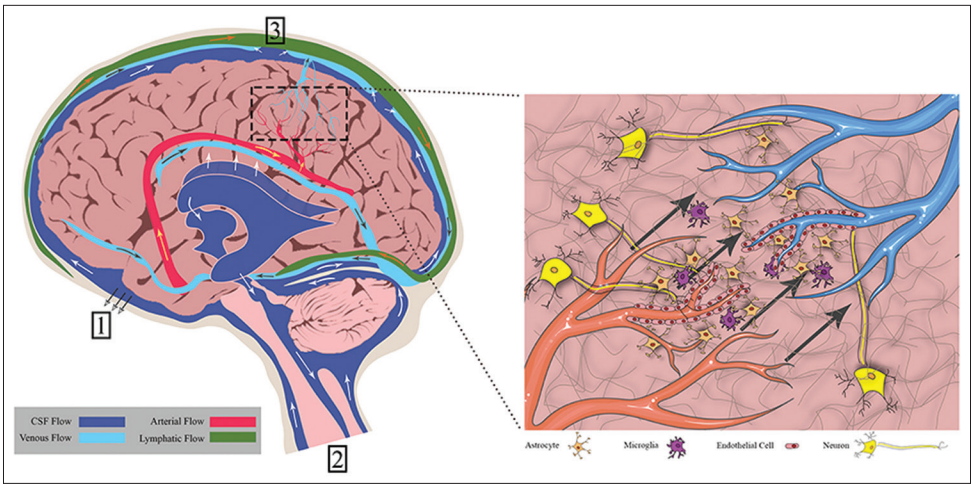

Figure 12: Convection-enhanced delivery

- Nanoparticles with incorporated iron oxide
  Iron oxide crystals are incorporated into polymer matrices to create these nanoparticles.[45,47-49]

Receptor-mediated transport (RMT)

For the transportation of endogenous peptides, such as transferrin and insulin, the BBB expresses RMT mechanisms. The traditional carrier-mediated transporters (CMT), which move specific small molecule nutrients, vitamins, and hormones, work in tandem with the RMT systems. The RMT systems serve as entry points for big-molecule medications that are linked to endogenous RMT ligands, just as the CMT systems do for small-molecule pharmaceuticals with a chemical structure similar to an endogenous CMT substrate.

- Monoclonal antibody (MAb)

Molecule Genetic engineering is utilized to create humanized or chimeric versions of monoclonal antibodies, or Trojan horses (MTH). Monoclonal antibody against the human insulin receptor is the most effective antibody-based MTH that has been discovered to date. This antibody has recently been humanized and demonstrated to pass the BBB *in vivo* in non-human primates. The RMT systems are ligands for certain peptidomimetic MAbs. The receptor's epitopes that these BBB RMT-specific antibodies bind are situated apart from the endogenous ligand binding site. To transport an attached medication, protein, antisense agent, or non-viral plasmid DNA over the BBB, peptidomimetic MAbs function as MTH.

Additional applications might have to do with different neurotropic infections or illnesses of the brain (such as multiple sclerosis, Parkinson's disease, or Alzheimer's disease).

- *In vivo* brain imaging of gene expression

Nuclear medicine imaging methods, such as PET or SPECT, can be used to image gene expression in the brain with antisense radiopharmaceuticals that penetrate both the BBB and the brain cell membrane, allowing for *in vivo* imaging of brain gene expression.[50]

Transporter-independent mechanisms to circumvent the BBB

- Convection-CED

CED is a technique for direct local/regional microinfusion into brain tissue. Therapeutic drugs are distributed into the interstitial space through a continuous infusion pressure gradient that lasts for hours or days. The CED approach is mainly applied to large molecular weight agents, such as viruses, oligonucleotides, nanoparticles, liposomes, and targeted immune toxins that exhibit low BBB leakage and/or considerable systemic toxicity. The infusion parameters (rate, volume, duration, cannula size), infuscate characteristics (molecular weight, surface properties, tissue affinity), and tissue properties (tissue density, extracellular space, vascularity, and interstitial fluid pressure) are the factors that determine the CED volume of distribution. Studies on animals have shown that by incorporating contrast ants into the infusate, the volume of distribution attained by CED may be seen in real-time using magnetic resonance imaging.[51,52]

- Bradykinin receptor-mediated BBB opening

An endogenous peptide mediator of the inflammatory response called bradykinin has the ability to cause brief increases in blood vessel permeability that are particularly targeted to the vasculature surrounding tumors. The synthetic analog of 7 bradykinin, known as RMP-7 (lobadimil), is 100 times more powerful in mice than bradykinin and is selective for the B2 receptor.[50]

- Ultrasound (US)-mediated BBBD strategy

The US is made up of pressure waves with frequencies of at least 20 kHz. Ultrasonic waves can be focused,

reflected, and refracted through a medium much like optical and audio waves can. The low penetration of US through the skull has been a significant barrier to its use for BBBD, and for many years it was thought that to provide US treatments in the brain, the skull bone needed to be removed. However, by employing large surface area phased arrays, it is possible to achieve focal, trans-skull-focused US (FUS) exposure of brain tissue, as demonstrated by practical and theoretical research. Image-guided technology has recently advanced (such as magnetic resonance imaging (MRI)-guided).

Therapeutics may now be delivered to the targeted brain regions through the unbroken skull thanks to FUS clinical systems, and promising outcomes have been seen in both animal and human trials. Ultrasonic microbubbles in conjunction with FUS can be utilized as medication carriers for targeted administration, as seen in Figure 14.[52]

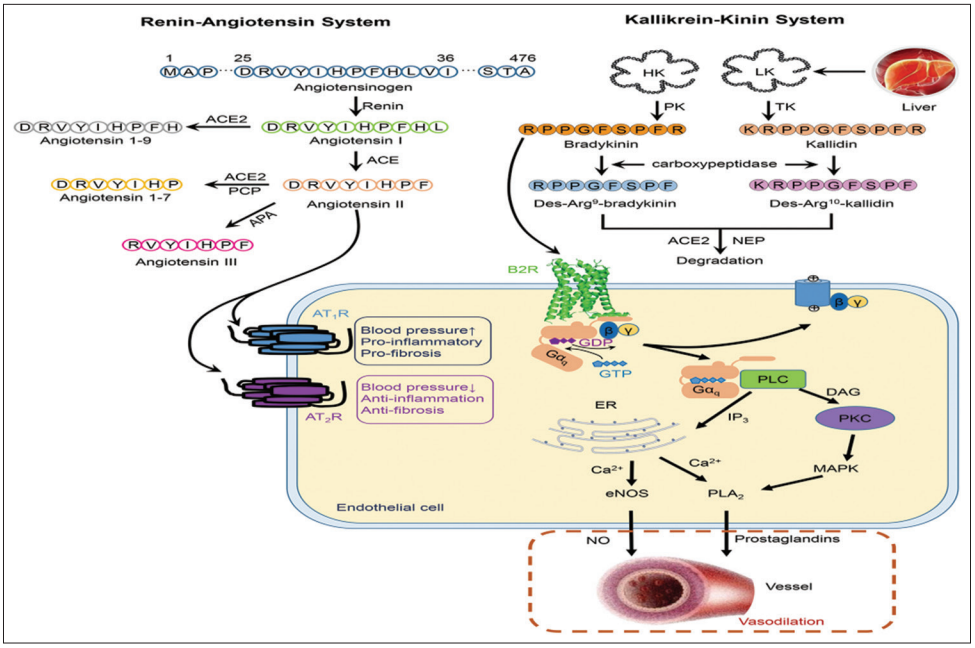

Figure 13: Bradykinin receptor-mediated BBB opening

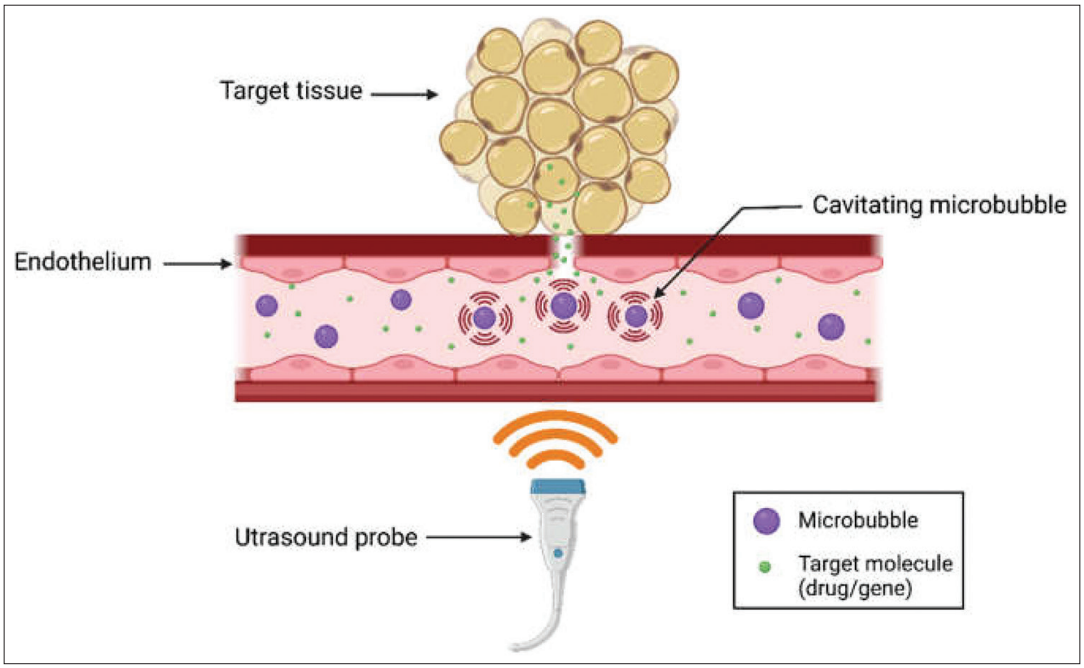

Figure 14: Ultrasonic micro bubbles for drug targeted delivery

CONCLUSION

This review focused on various diseases or disorders that occur related to the brain and their drug of choice. Most of the drugs are targeted in novel approaches the site-specific delivery at the target has been enhanced by overcoming the challenges of BBB. Drugs targeting through new technology i.e., nanoparticles could be better for improved therapeutic and diagnostic agents compared to many other therapies.

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