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Review on Drug Delivery Strategies to Overcome the Blood Brain Barrier

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ABSTRACT

One particular difficulty with drug administration to central nervous system (CNS) is the blood brain barrier (BBB). The Blood Brain Barrier is made up of an uninterrupted layer of specialized endothelial cells connected by pericytes, tight junctions, no fenestrated basal lamina and astrocytes foot processes. Therapeutic drug transport to the central nervous system is regulated and restricted by this intricate barrier. A number novel approaches have been investigated to improve the delivery of medication across the blood brain barrier. The crucial line separating brain tissue from in circulation is known as Blood Brain Barrier (BBB). Ion and molecular transport as well as homeostasis are regulated by special and protective properties of the BBB. This unique multicellular structure breaks down when any of this component are not maintained which subsequently encourage neuroinflammation and neurodeneration. The BBB is compromised in a number of high incidence disease, including stroke, Alzheimer's disease (AD)and Parkinson disease (PD).

Keywords: - Central Nervous System (CNS), Blood-Brain Barrier (BBB), nanotechnology, ultrasound, immunotherapy.

INTRODUCTION: -

The development process for CNS medications typically takes a lot longer than that of non-CNS drugs. CNS drug clinical trials are complicated by the brain's complexity, side effects, and the blood-brain barrier's (BBB) impenetrable nature.[1] Both small molecules and macromolecules are being researched as potential therapeutic agents to treat a variety of brain ailments; however, in addition to brain diseases, the absence of suitable technology to carry medications across the BBB limits CNS drug development.[2]The passage through endothelial cells is referred to as transcellular transport, and the degree of permeability in a healthy blood-brain barrier is determined by the balance between paracellular and transcellular transport.[3]This formulation's capacity to accumulate into particular regions can be useful in the creation of novel therapeutic approaches.[4]This makes it possible for blood's protein constituents, such as albumin, which is harmful to neural tissue, to enter the brain parenchyma. [5]group of five centers published a paper in 200 detailing their treatment of 221 adult patients suffering from brain metastases, low grade gliomas, high grade gliomas.[6]More than 10 billion capillaries make up the intricate circulatory network that makes up the human brain.[7]The tight junctions connecting the CNS's endothelial cells are the main component in the formation of the blood-brain barrier (BBB), a physical barrier that limits solute transit. [8]More than 60% of all marked medicines are recognized by these active efflux transporters, which also play a role in drug resistance. Using an in situ rat brain perfusion approach, they evaluated three prodrugs. Comparing the phenylalanine prodrug to other prodrugs, it demonstrated superior receptor affinity and brain absorption.[10] Another obstacle to cell- mediated delivery is the ability of the cell to regulate the release of the therapeutic drug in terms of both space and time.[11]The intranasal route has also been investigated as a noninvasive way to deliver medications to the brain within the last ten years.[12]In certain instances, such as ischemic stroke or traumatic brain damage, it is evident that the breach of the blood-brain barrier is a direct result of the occurrence.[13]To sum up, this work demonstrates that DA NPs can mitigate the toxicity linked to bulk dopamine and offer a fresh approach to treating Parkinson's disease.[14]Human neuro-progenitor cells were found in the brain after an intracarotid artery injection in the sole research showing stem cell entrance into the brain following pFUS- mediated breach of the blood-brain barrier.[15]

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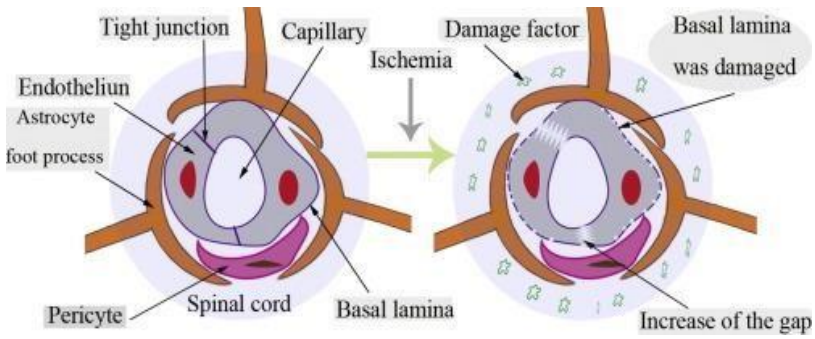
Strategies across the Blood Brain Barrier

Method	Route	Pros	Cons
Osmotic Disruption of BBB	Paracellular	Transient	Invasive Transient cerebral edema Non-specific
Chemical Disruption of BBB	Paracellular	Transient	Conflicting results in clinical trials
Enhanced Transcellular Transport	Transcellular	Targeted	Low efficiency
Nanoparticle Delivery	Paracellular and Transcellular	Targeted Sustained and/or controlled release	Cost Regulatory hurdles Potential toxicity
Cell-Based Delivery	Transcellular	Targeted	Toxicity to cell carrier Low therapeutic loading
Focused Ultrasound	Paracellular and Transcellular	Non-invasive Targeted	Cost
Intrathecal and Intraventricular Delivery	Bypass BBB	Elevated concentrations in CSF	Invasive Limited parenchymal concentrations Rapid CSF turnover
Intranasal Delivery	Bypass BBB	Non-invasive Simple administration	Irritation of nasal mucosa Low efficiency
Interstitial wafers and microchips	Bypass BBB	Sustained and/or controlled release	Invasive Limited distribution through ECS
Convection Enhanced Delivery	Bypass BBB	Enhanced distribution via bulk flow	Invasive back flow of infusate

The One of the several Barriers including: -

I) Blood spinal cord barrier: -

keeps the CNS parenchyma and intraspinal blood vessels apart. The specialized tiny blood arteries that round the spinal cord provide a semipermeable anatomical contact. It serves as a functional and anatomical barrier to keep dangerous substances out of the brain. A physical barrier that separates the spinal cord parenchyma from the blood, keeping pathogens, poisons, and blood ells out of the spinal cord and preserving the carefully regulated chemical equilibrium in the spinal environment that is essential for healthy neurological development.



Arachnoid barrier:

The avascular arachnoid epithelium, which is located beneath the dura mater, makes up this barrier. Layer of cells in the meninges that controls the flow of chemicals and cells into and out of the cerebrospinal fluid (CSF) and divides it from the durometer . The arachnoid, an avascular membrane that is positioned between the dura and the pia, participates in the metabolism of cerebrospinal fluid (CSF) through the subarachnoid space.

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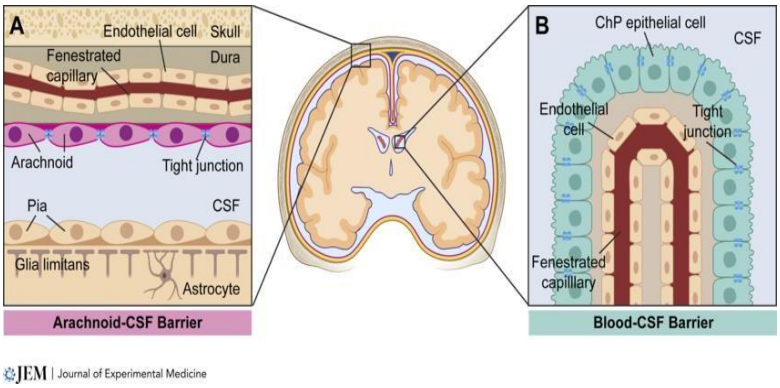


Blood - cerebrospinal barrier: -

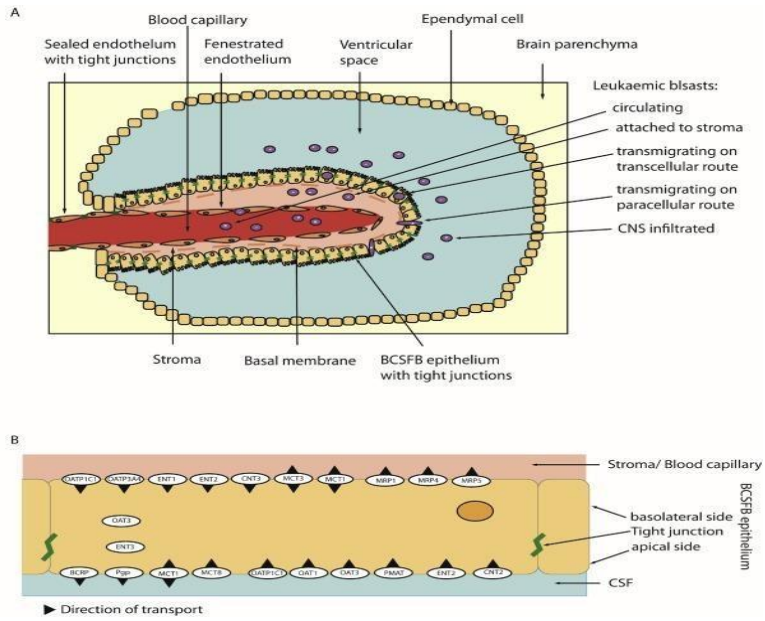
physical and chemical barrier that divides cerebrospinal fluid (CSF) from blood. It may include

I) Choroidal epithelial cell - located at choroid plexus

ii) Basal membrane - it is the part of CSF

iii) Endothelium capillary - capillary contains fenestration.

It serves as a functional and anatomical barrier to keep dangerous substances out of the brain. It is a defense mechanism in the central nervous system (CNS) that filters blood contents. It is mostly made up of membranes in the choroid plexus that divide blood from CSF.



iv) Choroid plexus barrier: -

The network of cells and blood arteries in the brain's ventricles, which are areas filled with fluid. Cerebrospinal fluid is a thin layer of cells that surrounds the blood vessels. The blood-CSF barrier, which separates blood from CSF in the brain, is maintained by the choroid plexus. The choroid regulates the eye's volume and temperature in addition to providing nutrition to the outer retina.

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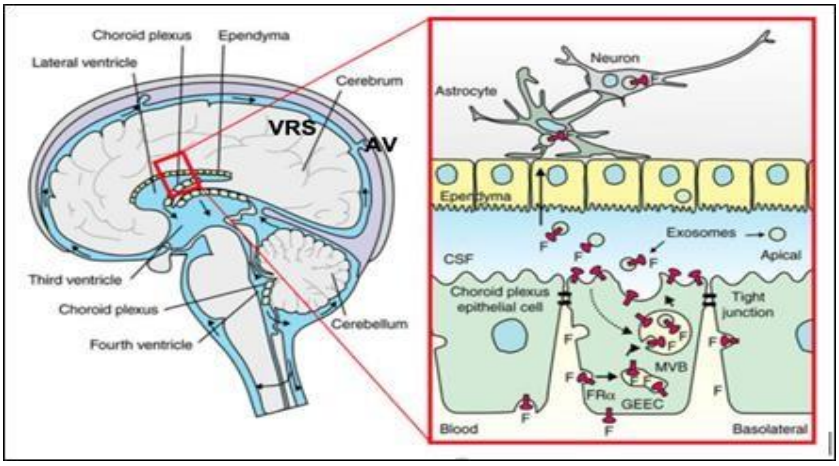

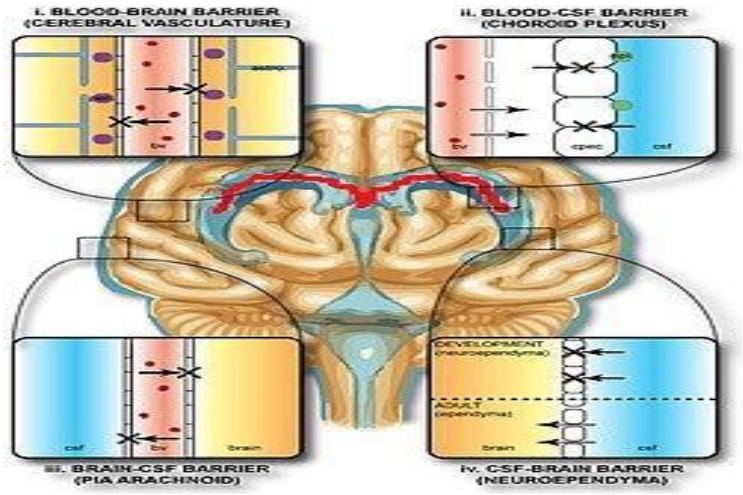

Combining image of Blood Brain Barrier

 # List of drugs can cross the Blood Brain Barrier: -

1) **Barbiturate**
2) **caffeine**
3) **Ethanol**
4) **Nicotine**
5) **Cephalosporins**
6) **Morphine**
7) **Diphenhydramine**
8) **Ketoprofen**
9) **Oxycodone**

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10) Naloxone

 # List of drugs which cannot cross the Blood Brain Barrier: -

1) Penicillin

2) Dopamine

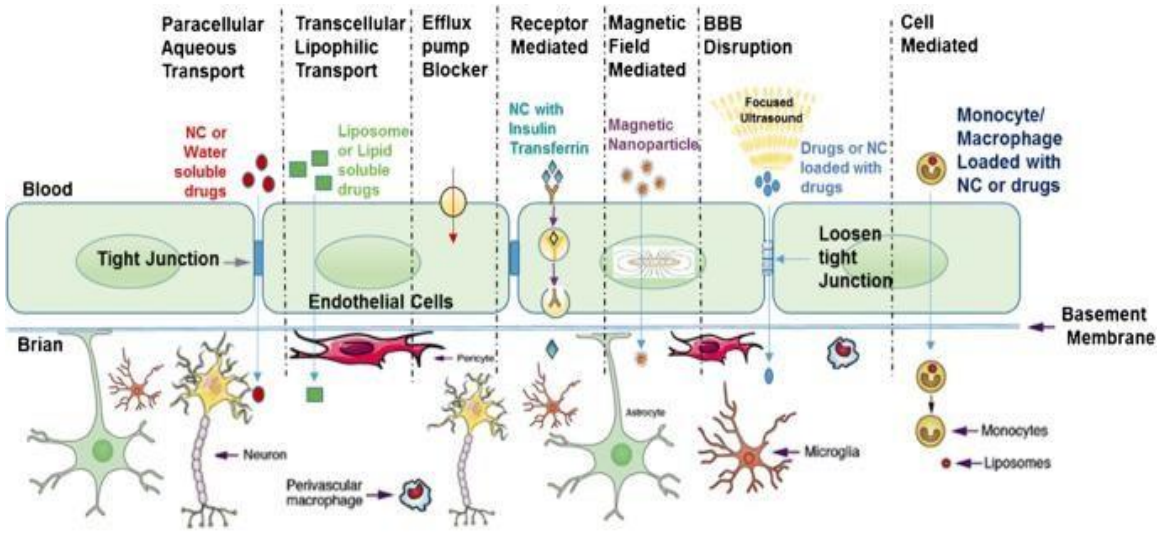
3) Cocaine

4) Methamphetamine

5) Heroin

Mechanism of Blood Brain Barrier: -

Endothelial cells (ECs), pericytes (PCs), capillary basement membrane, and astrocyte end- feet make up the blood-brain barrier (BBB), which is responsible for protecting the brain from toxins, removing dangerous chemicals from the blood and giving brain tissue nourishment.



Conclusion: -

Although the BBB plays a crucial role in the brain, treating CNS illnesses requires novel therapeutic strategies due to its presence. The need for better CNS therapeutic delivery will only grow over time due to the aging population and rising prevalence of neurological illnesses. Modern developments in medication delivery techniques are adding to our toolkit for treating central nervous system disorders. The blood-brain barrier (BBB) plays a vital role in the brain, yet because of its presence, treating CNS disorders requires novel therapeutic strategies. It will only take time for demand for better CNS therapeutic delivery to rise due to the aging population and rising prevalence of neurological illnesses. The arsenal of tools available to us for treating CNS illnesses is growing thanks to recent advancements in medication delivery techniques.

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