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ADVANCEMENTS IN DRUG DELIVERY METHODS FOR THE TREATMENT OF BRAIN DISEASE

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Abstract

The blood-brain barrier (BBB) has been a great obstacle for brain drug delivery. The BBB in healthy brain is a dispersal barrier essential for protecting normal brain function by impeding most compounds from transiting from the blood to the brain; only small molecules can cross the BBB. Under firm pathological conditions of diseases such as stroke, diabetes, seizures, multiple sclerosis, Parkinson's disease and Alzheimer disease. There are three types of barrier present in central nervous system such as Blood Brain Barrier, Blood Cerebra-Spinal Fluid Barrier, and Blood– Arachnoid Barrier. Alzheimer disease, Parkinson's disease, epilepsy, psychiatric disorders or neurodegenerative diseases, different types of drugs are available. But they have some lacuna for transportation of drug though these barriers and reaching drug to the target site. As an importance, several strategies are currently being sought after to enhance the delivery of drugs across the BBB.

Keywords: Blood-brain barrier, Parkinson's disease, Alzheimer's diseases, psychiatric disorders, multiple sclerosis, pathological conditions, stroke, diabetes, seizures.

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INTRODUCTION

Cellular barriers in the body act as a portal between the external environment and interior chambers. This is the occurrence for the epithelial lining segregationing the externally-exposed fundamental of the gastrointestinal (GI) tract and the bloodstream.[1-3] Cellular barriers also appear for the interface between the bloodstream and the parenchyma and cellular components of tissues and organs. This is the occurrence for the inner endothelial lining in blood vessels, such as the blood-lung barrier, the blood-brain barrier, etc [1]. The aptness to traverse these cellular barriers in the body is pivotal for efficient delivery of therapeutic and diagnostic agents into the circulation and tissues/organs where intervention is required [2]. Neurological disorders alongside the neuropsychiatric department include epilepsy, Alzheimer and other dementias, Parkinson's disease, multiple sclerosis, and migraine [3, 4]. However, only small molecules that are lipid soluble and have a molecular weight < 400 Da can cross the BBB; most macromolecules cannot creep into the brain endothelium. These advances emphasize the need for reappraising Examples of diseases together, amyotrophic adjacent sclerosis, Alzheimer's, Parkinson's, & Huntington disease with neurodegeneration (e. g. some concepts on brain drug delivery and reveal great opportunities for new strategies to deliver drugs into the brain.) The immediate significance of such condition is that several pathological disorders concerning CNS remain untreatable. Examples of diseases include neurodegeneration (e.g., amyotrophic lateral sclerosis, Alzheimer's, Parkinson's, Huntington disease, and prion disease), genetic insufficiencies (e.g., lysosomal storage diseases, leukodystrophy), and more than a few types of brain cancer [5].

TYPES OF BARRIERS

- **Blood Brain Barrier**: In the brain, brain capillaries are parted from brain by means of blood brain barrier. This barrier divorces the blood in the brain capillaries from brain tissues, together with the brain ECF & brain cells. Blood brain barrier (BBB) is the protective, highly selective semi-permeable membrane which is made up of endothelial cells. On the base of endothelial membrane, there are the special cells are present called as pericytes and astrocytes.Through this system molecules are allowed to pass by the passive diffusion and selective transport of several nutrients, ions, organic anions and macromolecules such as glucose, water as well as amino acids which play vital role in neural function [6].
- **The Blood Cerebra-spinal Fluid Barrier**: BCSFB viewpoints for Blood Cerebra-spinal Fluid Barrier. It divorces the blood in the brain capillaries from the CSF in

the brain ventricles. Exchange of compound is regulated in order to maintain a secure atmosphere for normal brain function. This BCSFB involves of the epithelial cells of the choroid plexus situated in the brain ventricles. These cells are strongly linked to each other by means of tight junctions. While the brain capillaries of the BCSFB have dissimilar to the BBB, comprehend pores and highly permeable.

- **The blood–arachnoid barrier**: Blood–arachnoid barrier is the separation between the blood in the blood vessels of the dura mater and CSF in the sub-arachnoid space. The blood–arachnoid barrier divorces the brain capillaries in the dura mater from the CSF in the sub-arachnoid space. The barrier is produced by a film of arachnoid cells which are associated by tight junctions. [7]

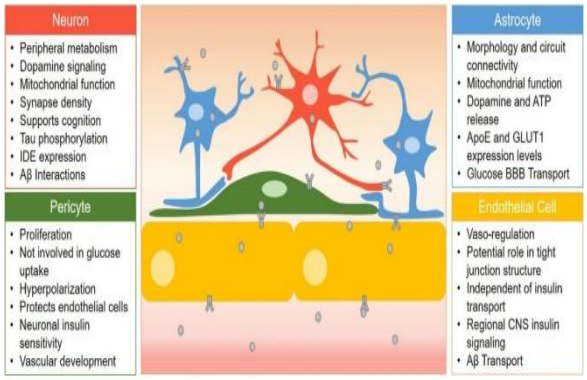

Fig 01. Mechanisms of transcellular drug that act on the BBB

FUNCTIONS OF BLOOD BRAIN BARRIER

- Selective barrier that allows nutrients to pass freely
- Is ineffective against substances that can diffuse through plasma membranes (example. Ethanol, caffeine)

Preoccupied in Some Areas

Ex.1) **Hormones rate of hormone secretion effectually**; there are specialized sites where neurons can "sample" the composition of the circulating blood. At these locations, the blood brain barrier is 'leaky' (pituitary gland) generally do not penetrate the brain from the blood, so in order to control the

2) **Capillaries of the choroid plexus**

- The BBB can break down under certain conditions:
- Hypertension, radiation, infection and brain trauma

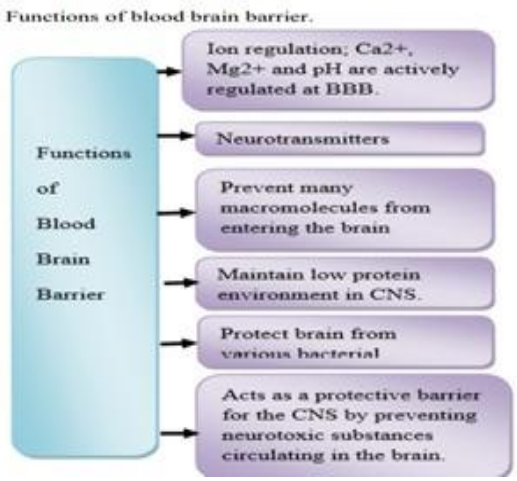

Fig 02. Functions of BBB

DIFFERENT PROPERTIES OF A DRUG AFFECTING ITS DISTRIBUTION

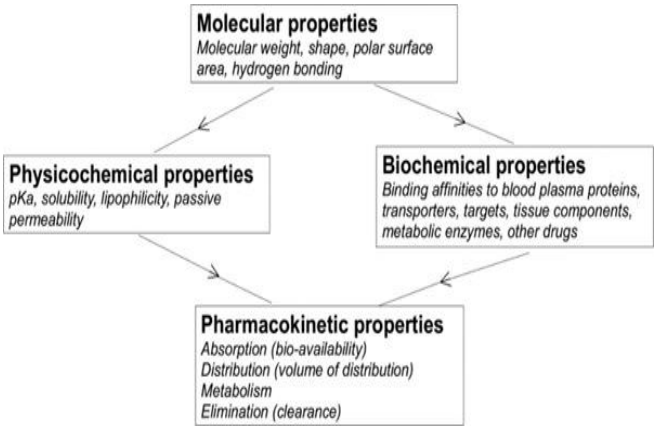

Fig 03. Different properties of a drug affecting its distribution

DISEASES RELATED TO BLOOD BRAIN BARRIER

1. Meningitis.
2. Sleeping sickness,
3. Brain abscess.
4. Parkinson's disease
5. Epilepsy.
6. Alzheimer's disease
7. Multiple sclerosis
8. Dementia
9. Neuromyelitis Optica
10. Myasthenia gravis etc. [3]

APPROACHES AND TACTICS FOR CENTRAL NERVOUS SYSTEM DRUG DELIVERY

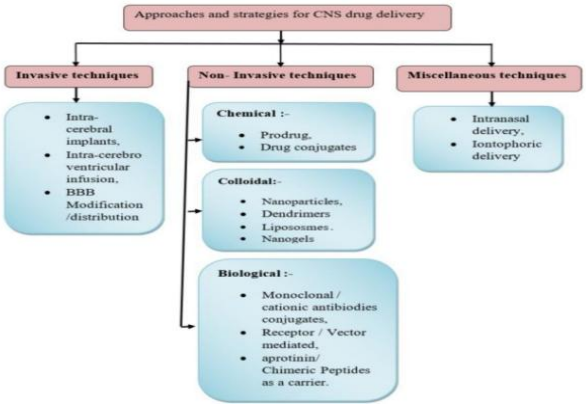

Fig 04.Approaches and tactics for CNS drug delivery **I.**

INVASIVE TECHNIQUES: SOME INVASIVE

Strategies are pragmatic for brain targeting. Temporary physiological disruption in the endothelial integrity of the brain is one of the invasive strategies for delivering drug to brain. It comprises techniques like Intra-cerebral implants, Intra-cerebroid ventricular infusion, BBB Modification /distribution [8].

i. **Intra-cerebral implants**

Chemotherapeutic agents administration through injections, placement of biodegradable, chemotherapeutic impregnated, wafers into tumor resection cavity, transmit over the diffusion to drive the drug into in filtrated brain.

ii. **Limitation of invasive techniques**

- It is very expensive process, requirements anaesthesia as well as hospitalization. It is non friendly course to patients.
- These techniques may advance tumor dissemination after successful disruption of BBB.
- In this technique, there might be chances of permanently damaging of neurons from uninvited blood component entering the brain [9].

iii. **Physiological tactics [approaches]**: Various tactics [approaches] are used for increasing brain delivery of therapeutics. Between all these approaches physiological approaches is most recognized method by the researchers because of advantage of transcytosis capacity of specific receptor expressed at BBB. Low density lipoprotein is the receptor related protein greatest adapted for such use with engineered peptide compound platform which incorporate the Angio peptide in new greatest advanced method with auspicious data in the clinic [10].

IV. **Non- Invasive techniques**: Non- Invasive techniques encompass pharmacological strategies capable of modifying drugs to assist transport across the BBB. Drug modification is done for enlightening lipid solubility and it is the most important factors for bypassing the drug through passive diffusion into the BBB. Drug transportation by using colloidal drug carriers is a most promising approach. Several colloidal carriers include in these techniques are emulsion, liposomes. Offensive, nanoparticles etc. it also includes coating of surfactants like polypropylene, polyethylene glycol, polyoxymethylene [10].

8. Nanoparticles

Nanoparticles are particles arisen in nanometer range i.e., below 100 nm. Nano- sized drug delivery system is very important and widely used as it offers moderately drug nature–independent carriage due to their capability to mask the physicochemical properties of the content. Various polymer-based delivery system such as colloidal carriers, nanocarriers and nano vectors are developed in which their most important feature is their size that ranges from 10–1000nm.

E.g.

- Marketed drugs such as steroids and diphenhydramine display infiltration through paracellular–transcellular transports are essential for uttering the quality of absorptivity in the BBB [10].
- Albumin nanoparticles improve BBB permeability

RECENT ADVANCES IN NANOTECHNOLOGY FOR BRAIN DRUG DELIVERY

- The SS team of universities of Michigan has advanced tools to diagnose & treat the most virulent forms of brain cancer.
- 20-200 nm diameter of probes encapsulated by biologically localized embedding in brain cancer targeting.
- Chimeric peptide technology.
- Lip bridge technology.
- Peptide radiopharmaceuticals.

CURRENT TACTICS TO DELIVER DRUGS INTO THE BRAIN

Great exertions have been taken to deliver drugs and diagnostic agents into the brain. Combined with current advances in BBB research, various new tactics have been exploited. This review summarizes the works published in the past five years. Some of them are still in a period of proof-of-concept.

VIRAL VECTORS

Viral vectors have a natural ability to infect cells with nucleic acids. The application of viral vectors for gene delivery to patients with neurological syndromes has been examined for over two periods. In general, the transfection effectiveness of viral vectors is high (e.g., 80%) [10]. Lentivirus, herpes simplex virus, adenovirus and adeno-associated virus (AAV) vectors have attained gene transduction in the brain. The limitations of using viral vectors for drug delivery include difficulties in manufacturing, high cost of manufacture, and, most significantly, the safety of viral vectors because of the death of patients in clinical trials [11]

NON-VIRAL

Nanoparticles With the arrival of nanotechnologies, nanoparticles have been proposed as an intriguing tool to potentially enhance drug delivery diagonally the BBB. Extensive reviews can be found somewhere else [12]. Furthermore, nanoparticles, because of their nano size (< 200 nm), could penetrate into 'leaky' tumor tissue to facilitate drug delivery rendering to the enhanced absorptivity and retention effect. Nevertheless, for brain drug delivery, observing increased drug concentration in the brain using nanoparticles does not unavoidably imply that the small size of the nanoparticles makes them cross the healthy BBB [13].

DELIVERY OF DRUGS THROUGH ACTIVE TRANSPORTERS IN THE BLOOD-BRAIN BARRIER

Endogenous amino acids enter the brain finished the transportation systems within the BBB. One attractive tactic on brain drug delivery exploits this knowledge to link drugs with amino acids that actively cross the BBB. Peura et al. synthesized trio amino acid prodrugs of dopamine to enhance brain acceptance through the large amino acid transporter in the BBB. They tested three prodrugs using an in-situ rat brain perfusion technique. Nevertheless, taking into account the size of amino acids, this generous of prodrug tactic could only be suitable for small molecules. For macromolecules such as proteins and siRNAs, amino acids could be too minor to change the alleyway of their acceptance, or macromolecules could be too big to pass the transportation systems.The phenylalanine prodrug showed better receptor empathy and brain acceptance than other prodrugs [14].

BRAIN PERMEABILITY ENHANCERS

Many molecules have established the ability to transiently open the BBB and permit high concentrations of systemically directed chemotherapeutics to reach the brain. One of the foundations for these molecules to open the BBB is based on

the transient disturbance of the BBB by decreasing expression of TJ proteins such as claudin-1, occluding and tricellular. Their initial application was for intraarterial mannitol with chemotherapy mediators to treat brain tumors. Currently, cereport (a. bradykinin analog) has been publicized to increase BBB permeability and consequently improve anti-cancer efficacy of co-administered anti-cancer drugs in animal models. Nevertheless, clinical studies failed to show a benefit of the co-administration in glioma patients.It is very likely that co-administration of a drug and a permeability accompaniment is insufficient to achieve the benefits of the accompaniment in humans, as shown in the previous cereport and regadenoson studies. Since the communication of the enhancers with the BBB is transient, co-delivery of both enhancer and drug by one carrier could be important to allow the drug to cross the BBB while the accompaniment opens the BBB.

DELIVERY OF DRUGS OVER THE PERMEABLE BLOOD-BRAIN BARRIER UNDER DISEASE CONDITIONS

The BBB has been recognized as a great hurdle in brain drug delivery for a long time. Although the BBB leakiness is known to evolve with some disease conditions, detailed knowledge such as duration and size of the BBB opening is not well understood. With advanced studies, new mechanisms have been discovered. For example, glutamate release in ECs promotes BBB permeability.Interendothelial connections are key structures to maintain tissue-fluid homeostasis in the healthy brain. Under certain disease conditions, proteinaceous fluid enters the interstitium through the disrupted Interendothelial junctions, consequently causing edema [15]. Recently, MRI has become a common non-invasive tool to study BBB damage in patients. Inflammation is one of the root causes of BBB disruption. MRI was applied to patients with cardiopulmonary bypass, which induces a systemic inflammatory response [16].

NON-INVASIVE TECHNIQUES TO ENHANCE BRAIN DRUG UPTAKE

Ultrasound has become a striking technique to enable drugs to cross the BBB in current years. Microbubble-enhanced diagnostic ultrasound (MEUS), a non-invasive technique, effectively helped drugs cross the BBTB by growing BBTB permeability in glioma. Claudins, occluding and JAMs are major proteins in TJs in the BBB.[17]Besides the BBTB, the BBB still remains a barrier for drug delivery in brain tumors. The combination of focused ultrasound (FUS) and microbubbles can enhance the permeability of the BBTB in brain tumor's as well as disrupt the BBB in the surrounding tissue. The expression of these TJ proteins could be abridged by ultrasound irradiation and microbubbles, temporarily opening the BBB without damaging the normal brain tissue. FUS and microbubbles were performed in both a rat brain tumor and the normal brain for doxorubicin delivery. They demonstrated that the combined technique increased the drug retention time in the tissue over 24 h while enhancing drug crossing of both the BBB and the BBTB. Moreover, it is interesting that MEUS was able to temporarily suppress P-gp expression [18].

ALTERATION OF ADMINISTRATION ROUTES

Intranasal route is an effective administration route to deliver drugs into the bran. In this approach, drugs bypass the BBB and enter the brain directly through the olfactory route. Many drugs used to treat human immunodeficiency virus (HIV) have low bioavailability because of the first-pass effect, and also have low permeability across the BBB. The CNS is reported to be the most important HIV reservoir site. Efavirenz was encapsulated into solid lipid nanoparticles by high-pressure homogenization to improve bioavailability and brain uptake. Efavirenz nanoparticles increased the concentration of efavirenz in the brain over 150-fold through intranasal administration compared to oral administration [19].

NANOPARTICLES FOR BRAIN IMAGING/DIAGNOSTICS

Nanoparticles have been lengthily studied for tumor imaging and diagnostics. Nevertheless, little research has attentive on brain imaging for CNS diseases, possibly due to the challenge of the BBB. Development of imaging technologies, especially in MRI and computed tomography (CT), has improved management and prognostication of neurodegenerative diseases. BBB disruption can be quantitatively assessed by using DCE-MRI in ischemic stroke patients.Multimodal MRI has also been used to track the energetic progression of the injury and BBB disruption after intracerebral hemorrhage, which is a significant cause of morbidityand mortality [20]. In addition to diagnostics and monitoring therapeutic effects, quantitative and visual assessment of increased BBB permeability may help select appropriate therapeutic interventions beyond the recognized time window. TPA is the first treatment for patients with acute stroke. However, tPA could induce hemorrhage. Studies using CT angiography exposed hemorrhage transformation was correlated with increased BBB permeability. CT could be a tool to assess the risk of hemorrhage before the tPA treatment [21]. Additionally, Gd-micelles, which were developed as an MRI contrast agent for tumorsimaging, were used to examine BBB permeability in a rat model. A significant contrast area in the MRI images was observed in the ischemic hemisphere, indicating the BBB permeability for macromolecules. Due to their large molecular weight, the Gd-micelles remained in the ischemic hemisphere [22].

INFLUENCE OF AGING ON THE BLOOD-BRAIN BARRIER

A neglected issue in the literature and research is the influence of aging on brain drug delivery. This section recapitulates a few verdicts from the literature. The BBB is comprised of brain microvascular ECs, astrocytes, pericytes, neurons, and basement membrane. Aging could affect these workings of the BBB. For example, studies showed that genes related to inflammation and scar formation were upregulated in aged astrocytes [23]. Furthermore, with age, astrocytes decreased the secretion of trophic factors that prevented neural degeneration [24]. Regarding these studies, Okoreeh et al. injected AAV5-GFP-hIGF-1 into the striatum and cortex in order to transfer the IGF-1 gene to astrocytes in middle-aged female rats. The results showed that IGF-1 genes assisted the

recovery of stroke-induced damage including BBB permeability and neuroinflammation. However, they did not compare this gene therapy of IGF-1 in rats of different ages. With age, astrocytes also decrease nutrition uptake in the brain (e.g., glucose) and the corresponding receptor expression in the BBB (e.g., GLUT-1 expression).The results demonstrated that NGF penetration across the BBB was significantly higher in the new born rats under hypoxic condition than in neonatal and adult rats; for the aging influence, NGF showed significantly higher permeation in neonatal rats compared to adult rats [25].

CONCLUSION AND FUTURE DIRECTION

This review has roofed types, functions & current strategies to deliver drugs to the brain in the past five years. To design effective drug delivery systems for brain diseases, thorough understanding of BBB disruption is necessary. With recent advances, in addition to the common technologies including viral vectors and nanoparticles, novel non-invasive techniques. Previously developed nanoparticles that target tumor's according to the EPR effect could be applied to brain diseases. Gliomas contain highly heterogeneous ranges in which permeability is usual in peripheral regions. Thus, a grouping of strategies penetrating both permeable and normal BBB might have to be considered. Additionally, further studies on the dynamics of BBB disruption will come out, further investigations are necessary for a better grasp of the mechanisms which manage this different NPs-mediated transport of the drugs to the brain.

However, the strong efforts to allow the translation from preclinical to concrete clinical applications are worth of the essential economic investments. Development of drug for the treatment of brain diseases is very challenging because delivery of drug molecules to brain prohibited by variety of physiological, metabolic, and biochemical complications. Many drugs are used for the treatment of neurological diseases, cancer, Epilepsy, Alzheimer's disease, Parkinson's disease, Myasthenia gravis etc. But it is very difficult for the drug to cross BBB and reach their cellular target in the brain. It has many other limitations, so that huge efforts are required to develop efficient targeting drug delivery system. Recently, several approaches are developed for preparing best drug delivery to treat CNS disorders. It is expected that imaginative drug delivery system should assist brain disease diagnosis. By using these strategies and approaches, successful results are assumed and there will be a novel generation of drugs delivery system functioning properly. Systematic overview by using classical pharmacology and nanotechnology to treating different CNS disorders are well explained through this review article.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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The authors have no conflicts of interest to declare.

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