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Crossing the Blood-Brain Barrier through Drug-Targeting: The Future of CNS Medication Discovery

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A B S T R A C T

In many clinical situations, most notably in the central nervous system (CNS)-related illnesses, the disrupted blood-brain barrier (BBB) affects proper CNS medicine delivery regulation. Despite its crucial role in controlling and safeguarding CNS molecular transport from neurotoxins, BBB drug-targeting for CNS medications receives little attention. With that, this review plans to offer a broader view of the BBB, its current condition within the healthcare sector, numerous creative techniques focused on medication delivery in the brain, and associated subjects from the past to the present. In an effort to pique the readers' interest in new ways of transporting pharmaceuticals to the brain through the BBB, this review revisits established publications further to understand the state of pathological drug discovery, recognize the existing CNS medicine delivery techniques, and know the reason behind the lack of global BBB infrastructure that limits CNS medication discovery's future.

Keywords:Blood-brain barrier; Pathological conditions; Blood-brain barrier disruption therapy

1. Introduction

Worldwide, CNS disorders are considered frequent, fatal, and undertreated ailments [1]. In the Philippines, Cerebrovascular diseases rank as the second cause of death from January to June 2021, followed by Neoplasm as third in rank and Diabetes mellitus in fourth place [2]. Due to the current surge in CNS-related diseases, particularly among the elderly, there is an expected increase in brain drug discovery in the following decades. However, due to the difficulty of pharmaceuticals penetrating the BBB, studies for novel CNS treatments have the lowest completion rates compared to other therapeutic sectors. The BBB acts as a barrier membrane in a normal healthy brain, blocking most molecules from crossing CNS circulation but under several circumstances, disrupted BBB occurs. Moreover, approximately 99 percent of large-molecule medicines cannot pass through BBB. On the other hand, small-molecule drugs are almost as terrible, with over 98 percent failing to work [3], making the production of CNS medications substantially delayed than developing other medicines. Aside from this, drug studies for brain pharmaceuticals grow problematic due to the human brain's sheer complexities, possible medication adverse reactions, the impermeable BBB, and inadequate BBB medication crossing techniques [1]. Adequate technology deficiency to transport drugs over BBB associated with the intricacy of brain disorders also causes the delay of CNS drug research. Despite this, there is currently no BBB drug-targeting program in place at any pharmaceutical business in the world [3]. However, genetic and environmental factors or other pathological concerns that mainly involve the process of cell regulation and biological matter present in our body cause the diseases mentioned above. The pursuit of treating these conditions has allowed various researchers to elevate the improvement of drug discovery to help improve the current threshold of the pharmaceutical industry. This review reexamines studies of BBB as a dynamic CNS molecule transporter and recent advances highlighting the need to reconsider some brain drug delivery concepts while also revealing exciting new CNS medication delivery opportunities.

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2. Brief overview on BBB

The human brain, in general, is among the essential organs in the body, consisting of billions of neurons or nerve cells that communicate through trillions of synapses. It is the fattiest organ in the human body, with 60% fat content. These fatty acids aid in the brain's performance and function. When it comes to fats, the BBB is lipid-soluble, making it one of the pathways for fatty acids to go from the bloodstream to the brain via diffusion or protein-assisted transport. Fats are carried to the brain, while non-fatty or foreign elements are severely limited in their ability to diffuse because chemicals need to pass through the endothelial cell to diffuse into the brain tissue. Throughout the ages, specialized medical professionals and scientists have been finding a way to treat specific diseases that help medicines diffused in the brain without the restriction of BBB. As a unique brain microvascular endothelial cells (BMVEC) system, BBB is vital in preventing toxic substances from penetrating the bloodstream and the CNS circulation [4]. A German physician named Paul Ehrlich discovered the BBB in the late 19th century. Through his experiment, he obtained answers by injecting a dye into a mouse's circulation, finding out that dyes covered the tissues of the mouse except for its brain. He concluded that the dyes showed a lower affinity for attaching to the nervous system. The BBB's functioning can become a liability for the body's drug surface dependency. Changing it in research has demonstrated minor improvement throughout drug discovery. The BBB is a second way of separating circulating blood from the brain's extracellular space. Only specific chemicals from the circulation move through the barrier, allowing only chemical additives to penetrate the CNS. It acts as a shield against neurotoxins, infections, and migratory neurotransmitters that reach dangerously high levels in the brain. As a result, the BBB is an essential biological barrier that strictly maintains the milieu of the CNS to ensure healthy neuronal activity. This barrier is critical to consider when developing treatments for various neurological conditions because disruption of the BBB can generate severe pathology in multiple diseases, and overcoming the BBB is a major stumbling block in novel CNS treatments discovery.

2.1. Normal functioning BBB

BBB acts as a barricade, keeping substances out of the brain and maintaining brain homeostasis. It consists of basal membranes, tight junctions, neurons, astrocytes, CNS pericytes, and endothelial cells in the microvascular system of the brain. All of which are necessary for appropriate brain function. Ions and solutes travel through passive transport paracellularly among surrounding cells. Different processes, including passive diffusion, transporters, and transcytosis, are part of the transcellular route and P-glycoprotein (P-gp) as efflux affect permeability [1].

a

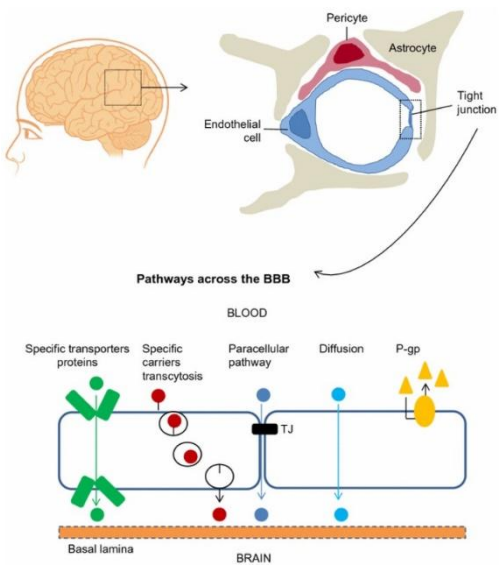

Fig. 1 - (a) normal physiologic condition of the BBB.
Source: Dong X. Current strategies for brain drug delivery. Theranostics. 2018;8(6):1481.

2.2. Disrupted BBB in pathological conditions

The BBB is disrupted in disorders like Cerebrovascular accident (CVA), Parkinson's disease (PD), Diabetes mellitus (DM), Acquired immunodeficiency syndrome (AIDS), Hypertensive encephalopathy (HE), Alzheimer's disease (AD), eclampsia, and other CNS-related traumas [5]. Due to its slightly flawed nature, certain minor vital water-soluble nutrients can diffuse freely over the BBB. In contrast, additional substances require particular transport mechanisms [6]. Many physiological barriers familiar throughout all neoplasms impede medicine transport via systemic CNS malignancies if the BBB is considerably impaired. A variable distribution of microvasculature across the tumor interstitial compromises medication delivery to neoplastic cells, resulting in spatially uneven drug delivery.

Furthermore, when a tumor grows more prominent, the vascular surface area shrinks, reducing the amount of blood-borne chemicals exchanged trans-vascularly. In this condition, the intra-capillary distance increases, resulting in a higher diffusional requirement for drug delivery to neoplastic cells. In the healthy brain tissue close to the cyst, there is increased hydrostatic pressure due to peritumoral swelling caused by increased interstitial tumor tension. As a result, the cerebral microvasculature in the brain, especially areas near a tumor, could have reduced permeability to pharmaceuticals compared to brain endothelium, leading to reduced extra tumor cell interstitial therapeutic levels[7]. However, in a study that focused on the role of oxidative stress on bipolar disorder, BBB disruption, whether temporary or permanent, is linked to a reduction in CNS protection and an increase in the permeability of proinflammatory (e.g., cytokines, reactive oxygen species) molecules from the peripheral circulation into the brain [6].

3. Blood-brain drug targeting

For most pharmaceuticals currently in use, drug activity does not center around how they accumulate an effect on the pathological organ or the cell around the body. Usually, the bioavailability of the drug spreads throughout the body, wherein the active component of the drug binds to the target site of action, crossing many biological barriers such as the cell membrane, cells, organs to deliver an effect [8]. The limitation behind this dilemma is a hindrance in providing the best treatment for the patient, the medicine or the pharmaceutical industry, and lastly, direct contribution to science and health. Drug targeting can bring a solution to all the problems present in the industry. The manifestation of it adhering to the principle of drug bioavailability and body system intervention is most likely to be achieved following appropriate measures. It will answer all the gaps about the said problem. Pharmaceuticals delivered in a targeted manner could have a positive impact. A significant improvement in current diagnostic methods in treating a wide range of disorders can likely positively affect the general population. For now, antibody-mediated diagnostics are the most common application of targeting procedures. If improvements may follow, the possibility is endless and would likely result in a more fostering discovery [8].

4. How drugs work on the BBB

4.1. Mechanism of action

Drugs can penetrate the BBB in different ways. The permeation process begins when passive transport of water-soluble substances crosses the BBB, which is modest because of the close links between the cells that line the interior of the blood vessels where tiny lipid-soluble substances get through the BBB by way of diffusion. Following that, highly specialized transport proteins transfer glucose, amino acids, and drugs over the BBB, while receptors receive and take proteins through the BBB. Finally, via the removal of nonnative substances from the brain, efflux transporters prevent passive diffusion [9].

4.2. Drug's conformity to the body

BBB, primarily based on physical factors, supplemented through the activities of brain to blood and enzymatic exchange, which is a significant barrier to medication delivery to the CNS. The vascular and cerebrospinal fluid barricades are the parallel barriers that make up the BBB (blood-CSF).Accordingly, three fundamental alterations to animal brain tissue inhibit the creation of a plasma ultrafiltrate within the Central systema nervosum. Rigid connections that bind oppositely positioned brain endothelial cells together, a low rate of pinocytosis, and a shortage of intracellular openings. In ideal circumstances, these changes restrict serum proteins from seeping uncontrollably into the CNS. However, employing a variety of routes, substances can still pass across the BBB [10]:

Diffusion through transmembrane. This type of diffusion allows most medications to pass across the BBB. Consequently, excessively fat-soluble drugs might get trapped in the capillary bed, preventing them from penetrating the cells beyond the BBB. Furthermore, lipid solubility promotes medication absorption in peripheral tissues, causing a drop in blood drug levels. Lipid solubility must then achieve equilibrium between enhanced BBB permeability and reduced blood concentration to optimize CNS medicine distribution.

Saturable transport system. Endogenous ligand-based transporter absorbed through the BBB via transmembrane diffusion results in roughly ten times higher absorption rate [11]. Furthermore, through transporters, various brain areas preferentially take up many regulatory chemicals, including short chains of amino acids and proteins for regulation.

The frequency during ligands transportation through BBB via saturable mechanisms is constantly modulated. The movement of the cerebral blood has functions of a flow-reliant compound like glucose have a high transit rate. BBB carriers respond to the essential requirements of the CNS during biological situations [12].

4.3. Drug distribution system

Amino acid transport system. Specialized transporters are required for CNS transportation of amino acids that cannot be produced in the body[13].

Monocarboxylic acid transport system. Acetoacetate (AcAc) and 3-beta-hydroxybutyrate (3HB), carboxylic, and some monocarboxylic acid molecules are prevalent in the CNS. At the BBB, specialized uptake and efflux carriers control their diffusion [14].

Cationic drug transport system. For lipophilic cationic medicines, transport methods through BBB may include a transporter-facilitated method in addition to passive diffusion [15].

Hexose transport system. Glucose, required for neural activity, is transported across the BBB by a particular carrier. The glucose transporter used in CNS medication transportation has a substantially larger efficiency at the BBB than other nutrient transporters, such as amine transport systems and neutral amino alkanoic and monocarboxylic acids [16].

Peptide transport system. Peptides have a significant affinity for water, are unstable and extensive that results to BBB penetration difficulty [17]. Specific peptides are carried to CNS via receptor, transport, and adsorptive-facilitated process [17,18].

Efflux transport system. Several studies on the relevance of the multimodal transporter P-gp were undertaken after identifying functional brain capillary endothelial cells and verifying it as a BBB medication efflux carrier. P-discovery gp's discovery transformed the rigid lipophilic protective layer in the BBB to a more operating state that controls compound transit between the brain and blood through active transport pathways [19].

4.4. Body-system intervention

Body's response. Drugs alter the BBB's stability, shape, and behavior by disrupting tight junctional (TJs) proteins, generating reactive oxygen species (ROS), causing cell damage, and triggering proinflammatory cytokines [20].

5. Pathological drugs' development gap on the current time

5.1. Relevance

BBB advancement follows a comprehensive procedure. All this commences with angiogenesis, when embryonic neuroectoderm emerges from previous vessels to form new vessels. Multiple BBB features are present within those initial sprouts, such as the development of tight junctions and nutrient transporters. Transcytotic vesicles and leukocyte adhesion substances are also present. As emerging arteries interact with pericytes and astroglia, the BBB's protective characteristics develop. TJ formation, reduced transcytosis, diminished expression of leukocyte integrins, and enhanced efflux channel activity are all examples. Interendothelial TJs are sealed and sustained throughout development and throughout the rest of one's life.

Numerous studies have been conducted better to comprehend the BBB's structural and functional distinctiveness. Immense proteome techniques have yielded information that aids in understanding the barrier's distinctive properties and the mechanisms that contribute to its creation, maintenance, and function in various disorders [21].

5.2. Environmental issues

Pharmaceutical firms that focus on research and development have emerged as leading companies in incorporating green chemistry and technology strategies into their production planning in recent decades, owing to cost and environmental concerns. In 1998, Anastas and Warner [22] came up with 12 principles of sustainable chemistry. Since then, the pharmaceutical industry has used them in the process design area and now they impact medicinal chemists in research and development laboratories.

5.3. Research, discovery, and development

During the time of herbalists and apothecaries, knowledge was obtained from simple empiricism. Drugs were only given out when they had been proven to be effective. Once recordkeeping remained accessible, such critical information was passed down orally. Despite the fact that we have better expertise than herbalists in the 1st century, the procedure of novel drugs is nearly comparable theoretically. Due to the low success rate, R&D teams at research pharmaceutical companies will examine multiple substances at various stages of the development cycle. The research pipeline of a multinational firm might contain anything from one to two hundred substances [23].

5.4. Impact to the pharmaceutical industry

The pharmaceutical industry has some distinctive structural and commercial procedural qualities that are unexpected beyond the sector yet have a big influence on getting innovative drugs to patients. The development of innovative drugs requires time and expensive procedure with a low success rate. Environmental impacts, corporate concerns that limit the enterprise, technological improvements in the sector, such as and the creation of an ecologically friendly pharmacy, were all discussed.

5.5. Pharmaceutical industry's environmental impact

The pharmaceutical industry's environmental impact was widely assumed to be negligible until the late 1990s. The ecological implications exclusively caused by manufacturing facilities were relatively small and with strictly regulated emissions; thus, deemed unproblematic. Currently, pharmaceuticals can be found in the environment in distinguishable ways: in sewage, particularly toxic and harmful chemicals emitted from manufacturing facilities, the disposal of wasted drugs, and the urine discharge of patients that undergo various treatments. Although it is difficult to quantify each medication, there is

global agreement that the latter source accounts for the vast majority of global environmental consumption, wastewater discharges and discharge of old medications accounting for only a modest portion.

5.6. Access to medicine

A small percentage of the population will invariably be affected by a large number of life-threatening diseases. However, because there aren't enough patients to support the expenditures, few commercial organizations can afford to study. Quantified economically viable regions grow in tandem with the length and expense of discovery. Useful intellectual property period, on the other hand, is getting shorter. As a result, numerous enactments have been passed. This changes the regulations on licenses, taxes, and reimbursements for promotion of research and development commercially practical for orphan diseases [24].

In early 2003, further related problems arose. Aside from finding adequate potential patients, the other criterion is the capacity to pay sufficiently, which has become a huge ethical challenge for drug companies. Although least evident, it determines which illnesses receive care. Patients' inability to pay for therapy makes drug research for such disorders a low priority[25]. Disagreements about international patent rights and health emergencies led to the Doha Declaration on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) and Public Health. Several unique drugs are now available in underdeveloped nations for a quarter of the cost in developed countries.

Patients in impoverished countries are not the only ones who face difficulties due to pharmaceutical pricing. In most nations, the government has some control over pharmaceutical pricing. In certain circumstances, increased downward pressure on cost and reluctance to prescribe new medicines was because both national and private health services companies are under strain. Such economic data is used to help companies decide which research topics to pursue, leading to an increase in the number of orphan illnesses, which is bad for patients.

6. BBB being underdeveloped in both academic and industry laboratories

The bottleneck in brain medication research, BBB, is one of the most crucial obstacles that restrict neurotherapeutics growth. In effect to the CNS, it partially blocks the delivery of CNS curative compounds and passage of a vast scope of drugs, to be specific; antibiotics, antineoplastic agents, or neuropeptides, via endothelial capillaries to the brain [26]. To close the gap with the worldwide market for cardiovascular medications, the international production for CNS pharmaceuticals would need to rise by over 500% [27]. Since most drugs cannot penetrate the BBB, the worldwide market for brain pharmaceuticals slows the progress of growth. Specifically, a limited percentage of molecularly small medicines with a mass of 400 to 500 Daltons and lipophilic passes through the BBB [3]. At the moment, there are no recombinant proteins, monoclonal antibodies (mAbs), gene therapeutics, or antisense can get past the BBB, only the lipid-soluble small molecules can penetrate the BBB.

Multiple medication delivery techniques were developed for CNS illnesses; however, the preponderance is obtrusive and lacks specificity. Few of them are delivered intranasal, direct neurological injections, or structural disruptions of the BBB using ultrasound [26]. Moreover, hardly 5% of the estimated 7000 medications in the CMC database are CNS-targeting, and these drugs exclusively treat depression, schizophrenia, and insomnia. Pharmacotherapy has been ineffective for several neurological illnesses [28]. Although treated with medicines, enzymes, and genes, many of these illnesses hold no industry-developed BBB solutions, resulting in its exploitation in creating brain therapeutics.

Furthermore, despite that L-dihydroxyphenylalanine is used to treat Parkinson's disease, a CNS-protective medicine produced to slow the disease's neurodegeneration has not been made or discovered [3]. Brain diseases such as Huntington's disease, Amyotrophic lateral sclerosis, and Alzheimer's disease are incurable neurodegenerative diseases. Patients with MS, on the other hand, are given cytokines, which are immune system proteins that effect on the central nervous system. Nonetheless, they play no role in terms of preventing the disease from progressing. For severe CNS disorders including cervical injury, cerebrovascular illness, or meningiomas, there is no effective treatment. Severe childhood disorders like lysosomal storage disorders (LSDs), autism, ataxia, and blindness have few effective treatment options. Even though the disease-causing gene is routinely discovered, BBB drug transportation remains the bottleneck in treating gene and enzyme replacement. Due to the outcome of the pharmaceutical industry's present belief, there is a disconnect between CNS medication development and drug delivery. Small molecules are thought to treat most brain disorders, and most small molecules cross the BBB, so today's pharmaceutical companies do not have BBB drug targeting programs [3]. According to Pardridge[27], the molecular and cellular biology of the BBB is unimportant to the neuroscience goal, and only a few neuroscientists are educated in BBB research each year. As a result, hiring BBB experts would be challenging for a primary pharmaceutical business. In the US, only a few BBB-trained scientists would be employed because only 1% of university neuroscience programs emphasize BBB transport biology [29].

On the academic side, Partridge [27] claims that BBB research has been underdeveloped in molecular neurosciences for a long time. For instance, approximately 0.1% of abstracts at the 30th yearly Gathering of the Society for Neuroscience which took place at New Orleans, LA, and the USA, were devoted to BBB research [27]. In an interview, he also noted that BBB drug transport is not taught in any academic neuroscience school in the US. He founded a biotech business that researched improved pharmaceutical distribution techniques across the BBB called Armagen since he was dissatisfied with the development. Currently, proteomics, genomics, as well as the detection of target genes and protein, are mostly employed to find blood brain barrier specific genes; however, the great promise for drug development seems to be largely untapped [30]. According to Partridge et al. [27], animals that had been experimentally induced to undergo an ischemic stroke were given an AGT-120 targeted on rats intravenously. Compared to intravenous BDNF alone, it decreased the amount of damaged brain tissue. Alternative ways for rupturing the barrier have also been devised and evaluated by neurosurgeons. Some neurosurgeons have had success injecting modest quantities of fluid directly into the brain tumor. Additional targeted strategies developed by neuroscientists have shown progress in animals. Some researchers employ the nasal and trigeminal nerves, which carry sensory stimuli from the mouth and nose, for nasal inhalation medication delivery. Others have investigated the use of ultrasound to vasculature's exposed, tiny portions. Through the work of Partridge's team and other researchers, the area of BBB medication delivery is exhibiting remarkable evidence of improvement.

BBB is a significant issue in brain drug development. The BBB problem has been disregarded for so long that there is minimal BBB infrastructure globally. Typically, the industry looks to academia for infrastructure support for significant areas of science, but academic neuroscience's long-standing negligence of the BBB field is rooted. As a result, the BBB issue requires industry leadership and infrastructure to ensure continued progress in this critical field. Furthermore, resolving the BBB would increase the number of small- or large-molecule pharmaceuticals eligible for CNS drug development by a factor of 1–2.

Additionally, this would increase the probability of developing novel therapeutics for incurable CNS disorders. The unpolished CNS markets are so big that the global neuropharmaceutical market's future growth could outpace the rest of the pharmaceutical industry. Improved brain drugs could save a lot of money in healthcare. US$40 billion is spent each year on stroke rehabilitation in the United States. Developing a neuroprotective agent for stroke could help cut that figure down even more [28]. As a result, increased spending on neuropharmaceuticals would reduce healthcare costs for chronic CNS patients.

7. Current medication delivery approaches for the brain [1]

7.1. Viral vectors

Viral vectors can use nucleic acids to infect cells. Patients with neurological problems were observed once viral vectors were used to transfer genes to them. The effectiveness of viral vectors in transfection is outstanding, about 80%.

7.2. Non-viral vectors

Nanoparticles are a possible technique for improving medicine delivery through the BBB. Multi-functionalization, the capability to transport drug payloads, drug release control, and medicinal pharmacokinetics modification are benefits of nanoparticles in general. Additionally, due to their nanoscale level (less than 200 nm), nanoparticles could permeate cancerous tissues and display drug delivery through permeability surge as well as retention effect.

7.3. BBB methods through the use of nanotechnology

The brain, an intricate organ in the human body, must be safeguarded from atmospheric and external materials that could affect the internal and external percentage of neurons, causing nerve excitation impairments and errors in body processing systems. Nanotechnology, a field of knowledge and applied science involving multiple disciplines such as physics, chemistry, biology, and chemistry, indicates further development of atomic substances in the span of one to one hundred (1-100) nm. Nanotechnology also involves the manipulation of atoms, depending on the number, to center it into drug manifestation. Several studies have been involved in nanotechnology drug delivery.

Nanotechnology innovation could lead to unique perceptions of the capabilities in the brain connections and techniques in detecting and treating CNS-related illnesses as a product of integrated multidisciplinary efforts. Nanomaterials have unique qualities, including decreased dimension, enhanced compatibility with living tissue, more prolonged circulation of the blood, and less toxicity. It uses a developing delivery system to convey medicinal medicines to the brain properly. Some studied techniques include nano-vehicles like micelles, liposomes, nanoparticles, dendrimers to transport medicinal substances, vaccines, peptides, nucleic acids, and peptides.

Organic nanomaterials

Polymeric nanoparticles. Nanoparticles extensively exploited to construct drug delivery vehicles traverse the BBB because they offer suitable drug distribution qualities. Some of which are efficiency-targeting and controlled drug release. Also, nanoparticles avoid phagocytosis by the reticuloendothelial system, resulting in higher drug percentages in the brain.

Liposomes. Liposomes are circular artificial cells made up of solitary amphiphilic bilayers of lipid that encapsulate therapeutic compounds such as medicines and vaccines. Predominantly exploited for therapeutic effectiveness and safety of medication delivery, liposomes are used in brain cancer therapy to pass the BBB and transport sufficient medications to the brain.

Dendrimers. Dendrimers are a type of artificial molecule with specialized encapsulation capabilities and set molecular weights. Brain tumors, neurological illnesses, stroke, neuroinflammation, and circulatory arrest have all been treated with dendrimers.

Micelles. Micelles are amphipathic compounds with particle sizes ranging from 5 to 50 nanometers. Micelles occur suddenly in aqueous solutions at certain temperatures and concentrations levels.

Inorganic nanomaterial

Gold nanoparticles. The characterization of gold nanoparticles with medicinal macromolecules has been widely investigated in treating neurodegenerative illnesses.

Silica nanoparticles. The ability to attach different biological molecules to the centers of surface-modified fluorescent silica nanoparticle variants clearly shows considerable potential with utilizing nano-vehicles to transport drugs to the CNS.

Carbon nanotubes. Carbon nanotubes are a form of nanomaterial made of tubes of graphite sheets having dendrimer dimensions. With free ends or encapsulated fullerene caps, these can be mono-walled or have multi-layered walls. Due to the potential functionalization with specific chemical

components and altering physical and biological features, nanocarrier approaches excite the interest in carbon nanotubes. The photothermal activity of carbon nanotubes is employed in cancer treatment.

Because of the BBB, which protects the brain from outside molecules, drug targeting and transport to the brain pose significant hurdles. Pathological drug targeting is paramount not only in the brain but also in the pharmaceutical sector. Nanotechnology-based techniques are being explored extensively to breach the BBB and deliver a sufficient quantity of medicine to identified CNS portions. More study is required to understand better and regulate the BBB crossing mechanisms and increase the effectiveness of nanotechnology-based brain delivery systems.

8. Drug delivery through active transporters

The utilization of amino acids that actively cross the BBB and link it with drugs enhances brain uptake.

8.1. Brain permeability enhancers

Many compounds have been found to breach the BBB temporarily as it permits entry to the brain significant doses of efficiently delivered chemotherapy drugs. The transient interruption of the blood-brain barrier caused by the lowering of TJ protein synthesis was part of the reasons for using drugs to access our blood-brain barrier. Cereport, which is a bradykinin analog, has indeed been found in animal models to enhance BBB permeability and, as a result, to boost the co-administered anti-cancer drugs' anti-cancer effectiveness.

8.2. Non-intrusive methods

In the past few years, ultrasound is becoming a tool for assisting medications in crossing the BBB. Microbubble-enhanced ultrasound (MEUS) non-intrusively increases BBTB permeability, allowing drugs to penetrate the BBTB.

8.3. Adeno-associated virus (AAV) vector

The BBB shields the brain from medication and exogenous molecule harmful side effects [31]. However, drugs designed to treat neurological problems must reach therapeutic concentrations in the brain. Understanding the BBB's interaction with therapeutic molecules from the standpoint of physicochemical property space can aid in the development of more effective and efficient drugs. As we all know, due to the BBB, CNS disorders are among the most challenging to cure. Most therapeutic medications are virtually entirely blocked from entering the CNS. Among the current strategies being investigated, AAV vector-based gene therapy provides the prospect to solve this issue. In an increasing number of research studies, the safety and effectiveness of using AAV vectors have been demonstrated, establishing AAV vector development as a priority in the realm of gene therapy.

In humans, AVV vectors have demonstrated significant efficacy and the capability to transmit genes into the brain., although immunogenicity is still an issue. On the other hand, viruses cannot generally traverse the BBB passively, albeit they can transfer genes into the targeted cells. AAV9 was thought to be the most successful AAV serotype for passing into the BBB and transduction to CNS cells after IV injection in early research. The capability of aavrh10, isolated from rhesus monkeys, was comparable to, if not superior in contrast to, AAV9. AAV-PHP.B, a recently developed capsid, was forty times more potent than AAV9 at transducing astrocytes and neurons. AAV-PHP.eB, an altered variation of AAV-PHP.B, was discovered to preserve AAV-capacity PHP.B's to transduce astrocytes while increasing neuronal transduction [32].

8.4. MB-enhanced FUS-induced blood-brain barrier opening

Microbubble enhanced focused ultrasound-induced blood brain barrier opening produces various-hour schedule frames that are beneficial to drug delivery into the CNS and drug penetration and storage, especially in tumors. This approach offers an appealing option for raising the chemotherapeutic medicine concentration to manage CNS illness and brain malignancies [33]. This opening demonstrated that siRNA could be administered noninvasively through the striatum with mice subject to HD [34]. Hsu et al. [35] revealed that when viral vectors that are adeno associated were followed by this clearance, they could be delivered in a non-invasive method and directly into regions of the brain.

This method can give noninvasive, temporary drugs to specific parts of the brain without causing damage. Furthermore, various preclinical studies have been undertaken to explore its efficacy in big animals, its potential of being applied to a person's skull, another is its use as a sonication equipment's durability. Previous research has shown that such a pharmaceutical administration approach is acceptable for medical studies when utilized concurrently.

8.5. Intranasal (IN) administration

In terms of alternatives for the route of administration, the intranasal route has massive potential. Intranasal (IN) administration allows therapeutic drugs to get to the CNS and avoid the BBB directly. Many CNS functions can be controlled by medicines administered into the nasal cavity, which are carried by the olfactory and trigeminal nerves [36]. IN administration may efficiently escape the liver's first-pass metabolism, reducing drug buildup in non-targeting organs and, as a result, reducing systemic adverse effects. It has also become one of the most common medication delivery systems because of its several benefits, including relatively fast adsorption, quick onset, nonintrusive, nontoxic, and ease of use [37].

Many therapeutic medicines, such as enzymes, polymers, peptides, proteins, and other tiny molecules, have been transported into the CNS via the IN administration up to this point. In a study conducted in 2015 [37], the researchers developed mucoadhesive solutions for IN olanzapine administration. In a

transient focal brain ischemia experimentally induced in mice, IGF-I administered through IN drastically decreased neurocognitive destruction [38]. NGD via IN effectively corrected neurodegeneration in those with Alzheimer's [39]. Finally, mice with methotrexate in their CSF developed lesser neurological disorder. Notwithstanding, in the case of systemic delivery, this is not the case [40]. The IN pathway is a safe and efficacious way to transport medications to the CNS. The medications circumvent the BBB and reach the brain via the olfactory route when administered this way.

9. BBB disruption (BBBD) therapy

Disrupted BBB are disruption of CNS synapses [41] accomplished by osmotic disruption, bradykinin, or irradiation. BBBD increases brain transportation of antineoplastic medicines [42]. Neuwelt[43] also claimed that the BBBD procedure could deliver up to 10 to 100 times more drugs to the tumor and its surrounding area than standard chemotherapy.

9.1. Receptor-mediated transcytosis

The drug is delivered to the brain via receptor-mediated transcytosis, which creates a cluster among medicine and receptor-focusing entities. An innate, antibody-attacking, or mimetic peptide ligand receptors can all constitute this entity. Both aspects might be chemically connected, or the medication could be combined with the RMT-targeting ligand in liposomes or nanoparticles [44]. Insulin, LDP, and transferrin, produced by endothelial cells, were among the most studied CNS targets [45,46].

9.2. Anti-TfR antibodies

Plenty of in-vitro and in-vivo research using the Tf receptor have been conducted with the goal of distributing CNS medications. The two methods employed were liposomes containing Tf for detecting compounds and DNA delivery [47] and an iron-mimetic peptide as a ligand [48]. Because the existence of elevated concentrations of Tf necessitated competing with the natural ligand, anti-Tf receptor antagonists were produced as optional technique [49]. Protein synthesis has been shown to enhance the discharge of antigen-antibody complex at the basolateral portion of the BBB endothelial cells when the antibody's attraction for Tf is reduced [50].

Studies on the use of RMT strategies aided novel developments in potentiating CNS medication transportation [51]. Consequently, the latest studies show that particles bearing anti-Tf receptor antibodies and non-permeant medications can effectively bridge the BBB in treating neuropathic pain syndromes.

9.3. Anti-IR antibodies

Insulin is transported into the CNS through the insulin receptor insulin. Anti-IR antigens, in contrast to TrF, have been employed in CNS medication distribution. Essential enzymes were produced as treatments for hereditary diseases using fusion proteins. The fusion proteins designed to offer vital enzymes as therapies for genetic diseases were derived from a study of humanized anti-IR antibodies (HIRMAb) which achieved excellent CNS absorption and movement after following IV treatment in monkeys [52].

9.4. LDLR and LRP ligands

The BBB is thought to include a single transmembrane glycoprotein known as the low-density lipoprotein receptor (LDLR), which recognizes low-density lipoprotein molecules and encourages cellular uptake, as well as LDLR-related proteins (LRP), which mediate lipoprotein and other ligand transit through RMT [53,54]. Although LDLR and LRP ligands like melanotransferrin, which has a faster cerebral transfer rate than Tf[55], have been utilized to transport drugs into the CNS, LDLR pathway antigens have yet to be developed. Studies on the LDLR show that RMT targeting the LDLR family can effectively transport chemotherapeutic drugs to the brain.

10. Discussion

In summary, the BBB's role is to create and maintain a unique area that meets the demands of the CNS while also protecting it from dangerous chemicals. However, in pathological conditions, BBB is disrupted. If the BBB is significantly compromised, various physiological barriers familiar to every CNS illness inhibit medicine transport across the vascular system. In the oxidative stress pathophysiology of BD, BBB disruption connectedly relates to a decrease of CNS insulation and an increase in the penetration of molecules from the peripheral into the CNS circulation.

There are many ways for drugs to cross through the BBB. One of which is by transmembrane diffusion. The capillary bed separates and prevents liposoluble medicines from reaching the BBB. As a result, optimizing CNS medication delivery through lipid solubility must observe equilibrium between improved BBB permeability and lower blood concentration. Another way that drugs cross through the BBB is by a saturable transport system in which its uptake rate through BBB is much higher than transmembrane diffusion. Various techniques may be used to deliver medications to the brain, and the human body's mechanism also plays a role in how pharmaceuticals affect the formation and viability of the BBB.

The BBB, the bottleneck in developing brain drugs, impedes future neurotherapeutic growth. Today's pharmaceutical companies don't have BBB drug targeting programs because small molecules treat most brain disorders. The global market for brain drugs has grown slowly since most medicines cannot

get through the BBB. Moreover, the molecular and cellular biology of the BBB is irrelevant to the neuroscience mission, and each year, a small number of neuroscientists receive training in BBB research. On the academic side, BBB research has lagged in molecular neurosciences for a time. The BBB issue needs leadership and infrastructure to progress in this vital field. If the BBB were solved, there would be a 1–2 factor increases in the number of small or large-molecule pharmaceuticals that could be used to treat the CNS. This would make it more likely to find new treatments for incurable CNS disorders. There would be fewer healthcare costs for chronic CNS patients if more money were spent on neuropharmaceuticals. There could also be a lot of money saved in health care if brain drugs were better.

Therapeutic techniques to deliver drugs into the brain are in constant development, and researchers have discovered multiple ways that have shown great effectiveness. Nanoparticles provide active transporters, including AAV vectors, brain permeability enhancers, microbubble-enhanced diagnostic ultrasound, MB-enhanced FUS-induced BBB opening, and intranasal administration. Another practical approach is BBB Disruption therapy which includes Receptor-Mediated Transcytosis, Anti-TfR antibodies, Anti-IR antibodies, LDLR, and LRP ligands. All have been breakthroughs in our search to transport drugs to the brain. However, more can be done to improve these current approaches, and thus, further study is required.

A lot of effort has recently gone into better understanding the BBB's structural and functional uniqueness. Green chemistry and technology approaches have been implemented into the process design of pharmaceutical firms. However, despite the necessity for CNS medication research, pharmaceutical firms confront a challenge in conducting clinical trials due to patient availability, environmental limitations, and budgetary restraints.

11. Conclusion

New ways for delivering medications to the brain have been explored in the past years. A thorough understanding of BBB disruption is required to build successful medication delivery methods for brain illnesses. Current strategies were re-visited, such as vectors and non-invasive techniques. BBB disruption, whether temporary or permanent, is linked to a reduction in defense and pro-inflammatory chemical penetration elevation in the CNS. But can potentially be restored through BBB therapies such as Receptor-Mediated Transcytosis, Anti-TfR and Anti-IR antibodies, and LDLR and LRP ligands as these therapies center on the interrupted tight junctions in the brain. This review emphasized that the pharmaceutical sector faces a severe ethical quandary in thoroughly exploring the research and drug development for BBB due to insufficient financially capable CNS patients. Unfortunately, despite the availability of prospective persons with CNS-related illnesses, CNS ailment studies will be abandoned if the majority of these persons refuse to accept the presently offered treatment.

In conclusion, BBB's intricacy necessitates a comprehensive study about its medication transport tactics; however, it may provide a transformative chance for developing effective drug distribution strategies for various neurological illnesses. Furthermore, additional research is required to find solutions to the rising doubts of the pharmaceutical companies in pursuing the search for CNS drug development involving the BBB.

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