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Review on brain-targeted drug delivery

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Abstract

Brain-targeted drug delivery is a field of research that seeks to develop new methods for delivering drugs to the brain. This is done by overcoming the blood-brain barrier (BBB), a network of cells that tightly regulate the flow of substances between the blood and the brain. Most of the time lipophilic drugs are easily cross blood brain barrier but few of them less soluble in lipid therefore they don't cross the blood brain barrier. After review we concluded that we can easily improve the solubility of drug using various techniques and Brain-targeted drug delivery is a promising field of research that has the potential to revolutionize the treatment of brain diseases. With further advances, it is possible that brain-targeted drug delivery will become a standard treatment for a variety of brain diseases and disorders.

Keywords: Blood Brain Barrier; Brain-Targeted; CNS; Lipophilic drug; Challenges

1. Introduction

A highly controlled microenvironment is required to promote the normal functioning of the central nervous system (CNS). Te existence of a biological barrier at the blood to brain interface effectively separating the brain from the rest of the body was established after the finding of Paul Ehrlich when he noticed that a peripherally infused dye did not stain the brain tissue. His finding was further supported by later observation from his associate Goldman as he applied the same dye to the cerebrospinal fluid. It did stain only the brain tissue without extravasation in the periphery. These biological barriers are established by different cells at three key interfaces: the blood–brain barrier (BBB), blood–CSF barrier (BCB), and the arachnoid barrier.

The brain is a complex organ that is responsible for many important functions, including thought, memory, and movement. Unfortunately, many diseases and disorders can affect the brain, leading to a variety of debilitating symptoms. In some cases, these diseases can be treated with medication, but the brain's natural defenses make it difficult for drugs to reach their target cells. This is due to the blood-brain barrier (BBB), a network of cells that tightly regulate the flow of substances between the blood and the brain [1].

2. The blood-brain barrier (BBB)

The blood-brain barrier (BBB) is a semipermeable membrane that separates the blood from the brain. It is made up of endothelial cells that are tightly joined together, and it prevents the passage of many substances from the blood to the brain. This is important for protecting the brain from harmful substances, but it also makes it difficult to deliver drugs to the brain [2].

2.1. The structure of the BBB [3-4]

The structure of the BBB is composed of the following components:

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Endothelial cells: The endothelial cells that make up the BBB are tightly joined together by tight junctions. These tight junctions prevent the passage of large molecules and particles from the blood to the brain.

Pericytes: Pericytes are cells that surround the endothelial cells of the BBB. They provide structural support to the endothelial cells and help to regulate the permeability of the BBB.

Astrocytes: Astrocytes are glial cells that are closely associated with the endothelial cells of the BBB. They help to regulate the metabolism of the endothelial cells and to maintain the integrity of the BBB.

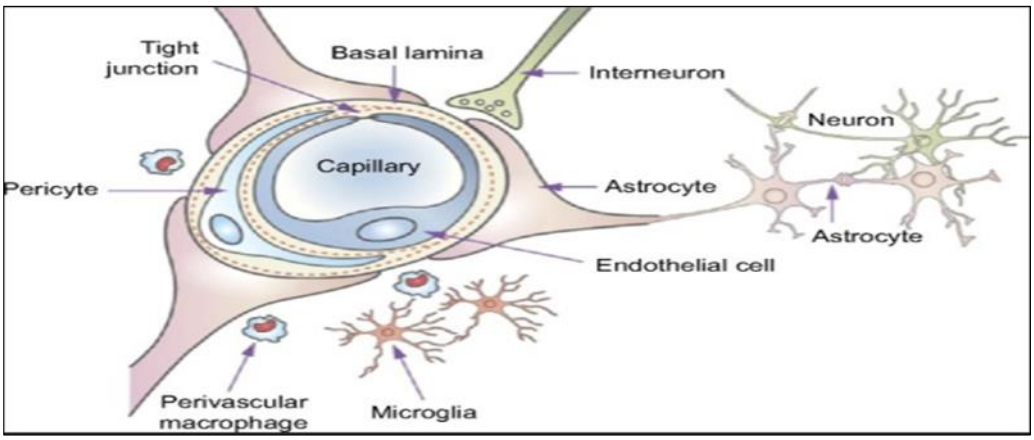

Figure 1 Structure of the BBB

Microglia: Microglia are immune cells that are located in the brain. They play a role in the defense of the brain against infection and injury.

Blood-brain barrier (BBB), is a fascinating structure that protects the brain from harmful substances and maintains its optimal environment. The BBB is a layer of specialized cells that line the blood vessels in the brain. These cells are tightly connected by junctions that prevent most molecules from passing through. Only small and lipid-soluble molecules, such as oxygen, carbon dioxide, and hormones, can diffuse across the BBB. Other molecules, such as glucose, amino acids, and neurotransmitters, need specific transporters to cross the BBB. These transporters are regulated by various factors, such as metabolic demand, inflammation, and stress.

2.1.1. The BBB serves two main purposes

To protect the brain from toxins and pathogens in the blood, and to maintain a stable chemical environment for the brain cells. The brain is very sensitive to changes in pH, temperature, osmolarity, and ion concentrations. The BBB helps to buffer these changes and keep them within a narrow range that supports neuronal activity and synaptic transmission. The BBB also prevents the entry of immune cells and molecules into the brain, which could cause inflammation and damage [5].

However, the BBB is not a perfect barrier. Some areas of the brain have a more permeable BBB than others. These areas are called circumventricular organs (CVOs) and they are involved in sensory and secretory functions. For example, the area postrema is a CVO that detects toxins in the blood and triggers vomiting. The median eminence is a CVO that releases hormones into the blood. The CVOs allow the brain to communicate with the rest of the body and respond to internal and external stimuli.

The BBB also changes with age, disease, and injury. Aging can cause the BBB to become leaky and allow more molecules to enter the brain. This can contribute to neurodegeneration and cognitive decline. Some diseases, such as Alzheimer's disease, multiple sclerosis, stroke, and brain tumors, can disrupt the BBB and cause inflammation and edema in the brain. Some drugs, such as alcohol, nicotine, caffeine, and cocaine, can alter the BBB function and affect the brain chemistry [6].

The BBB is a complex and dynamic system that plays a vital role in brain physiology and pathology. Understanding how it works and how it can be modulated is essential for developing new therapies for neurological disorders. In future posts, I will discuss some of the methods and challenges of studying and targeting the BBB [7].

2.2. Transport across the BBB

- **Passive diffusion:** In general, a wide range of lipid-soluble molecules can diffuse passively through the BBB and enter the brain.
- **Active efflux** Several ATP-binding cassette (ABC) proteins are expressed on the luminal, blood-facing endothelial plasma membrane of the BBB. They are ATP-driven efflux pumps for xenobiotic and endogenous metabolites, which limit the permeability of multiple toxins, including therapeutic agents.
- **Carrier-mediated transport (CMT):** The BBB isolates the brain and limits the diffusion of many essential polar nutrients, including glucose and amino acids, which are essential for metabolism. Therefore, other routes for the essential nutrients to reach the brain are necessary. CMTs are encoded genes within the Solute Carrier (SLC) Transporter Gene Family. This includes more than 300 transporter genes encoding membrane-bound proteins that facilitate the transport of a wide array of substrates across biological membranes.
- **Receptor-mediated transport (RMT)** The presence of peptide bonds limits the larger peptides and proteins from using the amino acid CMT systems to cross the BBB. However, specific neuroactive peptides, regulatory proteins, hormones, and growth factors get the use of RMT systems to cross the BBB. These Large molecular weight solutes can enter the CNS intact via endocytosis mechanisms in a process named transcytosis. Although most large blood borne molecules are physically prevented from entering the brain by the presence of the BBB and TJs, specific and some non-specifc transcytotic mechanisms exist to transport a variety of large molecules and complexes across the BBB. Tere are two types of vesicular transport systems; one is based on receptor-mediated transcytosis (RMT) and the other on adsorptive-mediated transcytosis (AMT). In RMT, macromolecular binds to ligands specifc receptors on the cell surface, which triggers an endocytotic event. Both receptors and their bound ligand cluster together, and a caveola are formed, which pinches of into a vesicle. Both ligand and receptors are internalized into the ECs and directed across the cytoplasm to be exocytosed at the opposite side of the cell . Finally, the ligand and receptor dissociate during cellular transit or the exocytotic event . While in AMT, positively charged large molecules interact with specifc cell surface binding sites that induce endocytosis and subsequent transcytosis.

3. Brain-targeted drug delivery

Brain-targeted drug delivery is a field of research that seeks to develop new methods for delivering drugs to the brain. This is done by overcoming the BBB and delivering drugs directly to the target cells. There are a number of different approaches to brain-targeted drug delivery, each with its own advantages and disadvantages [8].

3.1. Advantages of brain-targeted drug delivery:[8-9]

- Increased drug efficacy: By targeting drugs to specific cells in the brain, it is possible to increase the efficacy of treatment. This is because the drugs are delivered directly to the cells that need them, and they are not wasted on other cells.
- Reduced side effects: By targeting drugs to specific cells in the brain, it is possible to reduce the side effects of treatment. This is because the drugs are not distributed throughout the body, and they are not able to interact with other cells or tissues.
- Improved patient compliance: By targeting drugs to specific cells in the brain, it is possible to improve patient compliance. This is because patients are more likely to take their medication if they know that it is effective and that it does not have any side effects.

3.2. Disadvantages of brain targeted drug delivery:[8-9]

- One of the major disadvantages of brain-targeted drug delivery is the difficulty of crossing the blood-brain barrier (BBB), which is a complex and dynamic structure that protects the brain from harmful substances in the blood. The BBB has several mechanisms to prevent the entry of foreign molecules, such as tight junctions between endothelial cells, efflux transporters, metabolic enzymes, and immune cells. Therefore, only a small fraction of drugs can reach the brain after systemic administration, and most of them have low specificity and selectivity for their target sites.

  To overcome this obstacle, various strategies have been developed to enhance the transport of drugs across the BBB, such as modifying the physicochemical properties of drugs, using nanocarriers or prodrugs, targeting specific receptors or transporters on the BBB, or disrupting the BBB temporarily or locally. However, these strategies also have some drawbacks, such as increased toxicity, immunogenicity, instability, or cost of the drug

delivery systems, or potential damage to the BBB integrity and function.

- Another disadvantage of brain-targeted drug delivery is the heterogeneity and complexity of the brain tissue, which poses challenges for achieving uniform and optimal distribution of drugs within the brain. The brain consists of different regions, cell types, and microenvironments, each with distinct anatomical and physiological characteristics. Moreover, the brain is constantly changing due to processes such as neurogenesis, synaptic plasticity, inflammation, aging, and disease. Therefore, it is difficult to predict and control how drugs will interact with different components of the brain after delivery.

  To address this issue, some approaches have been proposed to improve the targeting and localization of drugs within the brain, such as using magnetic fields or ultrasound to guide or activate the drug delivery systems, or engineering the drug delivery systems to respond to specific stimuli or cues in the brain microenvironment. However, these approaches also have some limitations, such as requiring external devices or invasive procedures, or having low spatial and temporal resolution.

- A third disadvantage of brain-targeted drug delivery is the ethical and social implications of manipulating the brain function with drugs. The brain is not only responsible for vital functions such as cognition, emotion, and behavior, but also for personal identity and moral values. Therefore, altering the brain function with drugs may have profound and unpredictable consequences for individuals and society. For example, some drugs may enhance or impair certain cognitive abilities or emotional states, which may affect decision-making, learning, creativity, or social interactions. Moreover, some drugs may induce addiction or dependence, which may compromise autonomy and free will.

3.3. Some of the most common approaches include [10-11]

- Liposomes: Liposomes are small vesicles that can be used to encapsulate drugs. They can be modified to target specific cells in the brain, and they can also be used to increase the permeability of the BBB.
- Nanoparticles: Nanoparticles are also small particles that can be used to encapsulate drugs. They can be made from a variety of materials, including polymers, lipids, and metals. Nanoparticles can be designed to target specific cells in the brain, and they can also be used to increase the permeability of the BBB.
- Gene therapy: Gene therapy is a technique that can be used to deliver genes to cells in the brain. This can be done by using viruses or liposomes to deliver the genes. Genes can be used to express proteins that can protect cells from damage, or they can be used to silence genes that are involved in disease.

Despite the many advances that have been made in brain-targeted drug delivery, there are still a number of challenges that need to be addressed. One challenge is the development of new materials that can be used to encapsulate drugs. These materials need to be biocompatible and they need to be able to release the drugs in a controlled manner. Another challenge is the development of new methods for targeting drugs to specific cells in the brain. This is a complex process, and it is not always possible to target drugs to the desired cells.

Despite the challenges, brain-targeted drug delivery is a promising field of research. With further advances, it is possible that brain-targeted drug delivery will become a standard treatment for a variety of brain diseases and disorders.

3.4. Factors that can affect brain-targeted drug delivery [12]

Brain-targeted drug delivery is a challenging task due to the presence of the blood-brain barrier (BBB). The BBB is a semipermeable membrane that prevents the passage of many substances from the blood to the brain. This is important for protecting the brain from harmful substances, but it also makes it difficult to deliver drugs to the brain.

There are a number of factors that can affect brain-targeted drug delivery. These factors include:

- **The physicochemical properties of the drug:** The physicochemical properties of a drug can affect its ability to cross the BBB. For example, small, lipophilic drugs are more likely to cross the BBB than large, hydrophilic drugs.
- **The route of administration:** The route of administration can also affect brain-targeted drug delivery. For example, drugs that are administered intravenously are more likely to cross the BBB than drugs that are administered orally.

- **The use of a delivery system:** A delivery system can be used to increase the delivery of drugs to the brain. Delivery systems can be designed to target specific cells in the brain or to increase the permeability of the BBB.
- **The presence of disease:** The presence of disease can also affect brain-targeted drug delivery. For example, diseases that damage the BBB can make it easier for drugs to cross the BBB.

Despite the challenges, brain-targeted drug delivery is a promising field of research. With further advances, it is possible that brain-targeted drug delivery will become a standard treatment for a variety of brain diseases and disorders.

Here are some of the specific factors that can affect brain-targeted drug delivery:

- **Molecular weight:** The molecular weight of a drug is a major determinant of its ability to cross the BBB. Small molecules (< 500 Daltons) can cross the BBB by passive diffusion, while larger molecules require active transport or the use of a delivery system.
- **Lipophilicity:** The lipophilicity of a drug is also important for brain-targeted drug delivery. Lipophilic drugs are more likely to cross the BBB than hydrophilic drugs.
- **Charge:** The charge of a drug can also affect its ability to cross the BBB. Negatively charged drugs are more likely to cross the BBB than positively charged drugs.
- **Blood-brain barrier permeability:** The permeability of the BBB can be affected by a number of factors, including age, disease, and genetics. In general, the BBB is more permeable in infants and young children than in adults. The BBB can also be damaged by diseases such as Alzheimer's disease and multiple sclerosis.
- **Transport mechanisms**: The BBB contains a number of transport mechanisms that can affect the delivery of drugs to the brain. These transport mechanisms include passive diffusion, facilitated diffusion, active transport, and endocytosis.
- **Efflux transporters:** The BBB also contains a number of efflux transporters that can pump drugs out of the brain. These efflux transporters include P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated protein 1 (MRP1).
- **Target specificity:** The ability of a drug to target specific cells in the brain is important for brain-targeted drug delivery. Drugs that are targeted to specific cells are more likely to be effective and to have fewer side effects.

3.5. Challenges of brain-targeted drug delivery [13]

- **Overcoming the blood-brain barrier:** The blood-brain barrier is a network of cells that tightly regulate the flow of substances between the blood and the brain. This makes it difficult for drugs to cross the BBB and reach the brain.
- **Targeting drugs to specific cells:** It is difficult to target drugs to specific cells in the brain. This is because the brain is a complex organ, and it is not always possible to identify the exact cells that need to be targeted.
- **Developing new delivery systems:** It is necessary to develop new delivery systems that can carry drugs across the BBB and target them to specific cells in the brain. This is a challenging task, but it is essential for the development of effective brain-targeted drug delivery.

4. Conclusion

Brain-targeted drug delivery is a promising field of research that has the potential to revolutionize the treatment of brain diseases. With further advances, it is possible that brain-targeted drug delivery will become a standard treatment for a variety of brain diseases and disorders.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors have declared that no conflict of interests exists.

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