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Insignement to Brain Targeting of Drugs

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Abstract

Brain targeting is a bottle neck for the drug discovery scientist, due to its special protective system. The Blood Brain Barrier (BBB) and the blood cerebrospinal fluid barrier (BCFB) are not only protective barriers of the CNS but it can maintain the neuronal activity and functioning of the CNS This body protective system makes difficult to target the brain for the treatment of many CNS disorder. In the process of the better delivery system for the CNS many development has been made so far, but in the present scenario the emphasis on the eye has been in the developing stage. The eye is very sensitive organ of the body. Brain targeting through the ocular route is an intense task. Here in the various approaches has been summarized in three categories: Noninvasive, invasive and alternative routes of CNS delivery, moreover the factors affecting blood brain barrier been discussed.

Keywords

Brain and drug targeting; Ophthalmic route; Blood Brain Barrier

Introduction

The targeted delivery for central nervous system can be achieved by direct administration of the drugs in to the CNS [1]. Blood Brain Barrier (BBB) acts as a big obstacle in the distribution of drugs in to the CNS. The BBB plays major role in the selectivity of many of the drugs; moreover, it is well known that the hydrophilic drugs possess low affinity towards the BBB as compare to hydrophobic drugs. Brain targeting drug must cross the BBB or bypass the barrier, which will effect brain in efficient manner [2]. The BBB and BCSFB do not only protect the CNS against infectious agents and toxic agents, but also create an effect to the systemic drug delivery into the CNS [3]. The BBB and BCSFB functions are controlling the transfer of molecules between the blood and brain parenchyma and Cerebrospinal Fluid (CSF) [4]. It has been observed that CNS disorder is a difficult task due to the BBB and BCSFB. The Blood Brain barrier helps in transporting water and lipid soluble substances from blood circulation into CNS [5]. In the recent scenario, it is important to look into the most effective delivery system an ocular route for targeting CNS is important [3,4].

Overview of Blood Brain Barrier (BBB)

BBB acts as a dynamic interface. The approaches of the blood brain barrier have been used to increase the brain penetration. BBB is a major offend toward the brain targeted drug delivery [6]. The BBB protect the CNS from harmful substance [7]. The BBB maintained the volumetric and ionic environments and create the interference for systemic drug delivery to the CNS. The BBB plays important role in the conveying of lipid and water soluble substances from blood circulation into CNS [8]. The drug crosses BBB through the combination of endogenous compounds [9]. The low molecular mass (< 400-500 Da) with high lipid solubility substances have high capability to crossed the BBB, this phenomena is utilized to deliver the drug into the brain [5,10]. The BBB poses some differentiating features, which causes highly efficacious obstacle to the entry of chemical compounds into CNS [11]. It has the valuable ability to reduce and separate the human brain from circulatory network and allow only conveying of molecules that play the functional activity of brain [12]. The capillary endothelium of BBB acts as a permeability barrier [13]. The BBB has been started the creative path or convenience for better drug delivery to the brain [14].

Factors which affect the Blood Brain Barriers

Three factors mostly affect the blood brain barrier.

Metabolic barrier

The metabolic barrier is protected against the effect of bioactive molecules [15].

Anatomical barrier

In between CNS and blood free exchange of cells & solutes get restricted through this barrier [16].

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Transported pathways

The transport pathway provides the protection against xenobiotics and transports the biological substances like minerals, proteins, amino acids, vitamins, sugars, etc.

There are some factors of ocular drug delivery that affect the pharmacokinetics of the drugs and provide obstacle to target the brain through ocular route. The blood ocular barrier also provides protection from xenobiotics from the blood. Blood ocular barrier are two types 1) Blood-retina Barrier (BRB) and 2) Blood-aqueous Barrier (BAB) [17]. These barrier play first protection layer, however, the crossing this barrier, drug can be easily reached to the choroid and retina. This barrier is necessary for specific targeting. The brain disorders which are refractory to small drug molecule therapies are-CVS disorders, neurodegenerative disorders (Parkinson's disease and Alzheimer disease) and inflammatory disorders (Brain/spinal cord strokes) [18]. Approaches across the brain barriers are mentioned in Table 1.

Approaches across the brain barriers

Noninvasive techniques

The non-invasive techniques are classified into three methods.

Chemical method: In noninvasive techniques, chemical structure of drugs is transformed to improve physicochemical properties and functionalities. The prodrug method is used in chemical modification, where drug modified into the more lipophilic drug. In the chemical method after the latentiation both acetylation and hydroxyl groups are used to make to drug feasible to cross the BBB [20]. In chemical method three chemical drug delivery systems (CDS) are included-1) Enzymatic physicochemical CDS, 2) receptor-based CDS and 3) Site-specific enzyme-activated CDS. In chemical method, molecular packaging is used to increase the penetration of peptides through the BBB. In molecular packaging three steps are followed:

1. Increased lipophilicity to enhance passive transport.
2. Prevention of premature degradation by increasing enzymatic stability.
3. Exploitation of the lock to provide targeted.

Biological Method: The delivery of chimeric peptides by the receptor or vector is based on the use of a pharmaceutical peptide (Nontransferable). They joined with a transferable peptide which endures transcytosis interceded by receptor through BBB [21]. When the receptor gets bound to the receptor endocytosis gets initiated [22]. The nanoparticles avidness gets tuned to the focused receptor then its efficiency of this transcytosis regulated by receptor can be controlled. There is another technology which is regulated by cell penetrating peptide which is used to augment the delivery in CNS [23]. They operate through from unique mechanism which is receptor independent to interact with the surface of cells. They are also capable of transferring the molecules through the cell membrane which are attached to them. In process of target delivery many peptides have been used, but among the various peptides used, including Human Immuno Deficiency Virus type 1, herpes simplex virus type 1 etc., Trans-Activating Transcriptional (TAT) activator is the most reviewed [24].

Colloidal Drug Carriers: A colloid is a suspension of dispersed particles or droplets. Its range of particle diameter is about 1 to 1000 nm [25]. The colloidal drug carriers are liposomes, dendrimers, nanoparticles, micelles and emulsions. In colloidal drug carrier nanomedicines can go across the BBB by endocytosis and have been observed during the preclinical study for CNS conditions like HIV encephalopathy, acute ischemic stroke, brain tumors and Alzheimer's disease [26]. The blood distribution of colloidal particles influencing by the various factors like particle size, stability and surface affinity [27]. So far some colloidal carriers have been adopted for CNS delivery; they are single-walled carbon nanotubes and Polyethyleneimine (PEI) [28]. PEI is an organic polymeric molecule with a high cationic charge density due to the presence of multiple amino groups. Carbon nanotubes and PEI derivatives have been critically evaluated for gene transfer.

Invasive techniques

Only few nutrients and peptides can cross the BBB to achieve effective concentration within the brain tissue by the oral and intravenous route. These techniques has classified into four categories.

Intracerebral implants: Intracerebral implants is a highly traumatic drug delivery strategy which contain matrix and biodegradable polymer reservoirs. The polymer-controlled implants the strategy involves many advantages of the CNS delivery like low peak drug release limits tissue damage, biocompatible, low invasiveness, tunable release properties, sustained drug delivery, and localized delivery [29]. The disadvantage includes dosage limited by implant size and poor drug penetration. Intracerebral implants are also used in chemotherapeutic [30].

Intraventricular delivery/interstitial delivery: The blood brain barriers deliver the drug directly into the Intraventricular delivery or the interstitial delivery system. The anticancer drug has been administered locally to obtain the drug concentration for longer period. [31,32]. In various clinical trials, some drugs like methotrexate and nitrosourea were used. The disadvantages of this strategy are catheter obstruction, CNS infection and inadequate drug distribution [33].

Biological tissue delivery: In this tissue implants delivery technique into the brain is used to modulate naturally secreted therapeutic agent. This tissue delivery is used for the treatment of Parkinson's disease [34]. Transplanted tissue cannot be present to a lack of neovascular innervations. In these techniques foreign tissue is improved for culturing distinct cell types.

Blood Brain Barrier Disruption (BBBD): Blood brain barrier disruption strategy is an independent part of invasive techniques. BBBD therapy is an intensive and effective way of sending medication to brain tumors. In BBBD hyperosmolar mannitol solution is used as additive. BBBD can increase the permeability of the BBB by shrinkage of cerebrovascular endothelial cells followed by production of disrupted inter-endothelial [35]. The BBB enduring to this agent, such as lactamide, saline, urea, radiographic contrast agents, hyperosmolar solutions of Arabians and mannitol.

Alternative routes for CNS drug delivery

The alternate approach for CNS can be characterized in to intranasal and iontophoric delivery system.

Intranasal delivery

In Intranasal drug delivery nanoparticles are used. In the cardiovascular system intranasal route is an alternative route. Noninvasive drug delivery to the CNS neural pathways is joined to the nasal mucosa and the brain and provides the potential routes for targeted delivery [36,37]. The nose-to-brain pathway is suitable for the quick delivery of the therapeutic agents to the CNS within

Noninvasive Techniques	Invasive Techniques	Alternative routes for CNS drug delivery
Chemical Method	Intracerebral Implants	Intranasal Delivery
Biological Method	Intraventricular Delivery/ Interstitial Delivery	Iontophoretic Delivery
Colloidal Drug Carriers	Biological Tissue Delivery	
	Biological Tissue Delivery	

Table 1: Different approaches across the brain barriers [19]

the minutes. Low molecular weight and higher lipophilicity drugs are prone to intranasal uptake into the CNS. The physiochemical properties of small molecules such as size and lipophilicity majorly affect the efficiency of CNS delivery for intranasal administration. In nasal pathology mucosal irritation should be avoided [38].

Iontophoretic delivery

Iontophoresis is a method for delivery of ionized molecules across the BBB through an externally applied electric current [39]. Iontophoresis devices are used primarily for the treatment of inflammatory conditions in the skin, muscles, tendons and joints (temporal-mandibular joint dysfunctions). Noninvasive Iontophoretic devices are used to deliver the drug into the CNS. The Invasive method and noninvasive method Iontophoretic devices are also used for increase macromolecule agent delivery to the brain.

Pharmacokinetics of ocular route

Lachrymal fluid barrier

Drug absorption of lachrymal fluid in the eye gets restricted due to the presence of corneal epithelium [40]. Hydrophobic drugs have huge affinity across this barrier than hydrophilic drugs [41].

Blood ocular barriers

This barrier implement the protection from xenobiotics to the blood. Blood ocular barrier constitutes two types of barriers: Blood Aqueous Barrier (BAB) and Blood-Retina Barrier (BRB). After passing this barrier, drug can be easily arrive to the choroid and retina. For this specific targeting is required [6].

Loss of drug through ocular surfaces

The lachrymal fluid attempt to remove installed drug rapidly within a minute from ocular surface after instillation [42]. The elimination due to lachrymal flow declines the concentration of the drug in the blood. For that reason, ocular bioavailability of the drug in tear fluid becomes only 10% [43].

Conclusions

Brain targeting is a challenging task as delivered drug gets prohibited across the brain. The suitable and effective approach of drug delivery to the brain may facilitate the drug to the brain for effective CNS treatment. An improvement in the passive permeation of the BBB has an important role to play the drug delivery science. In search of better targeted delivery, the intranasal route with nanoparticles found effective through biological tissue for the treatment of Parkinson's disease**.** Here in we discussed various approaches including ocular route and factors, which affects the BBB permeability.

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