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Review article

Progress in brain targeting drug delivery system by nasal route

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ABSTRACT

The blood–brain barrier (BBB) restricts the transport of potential therapeutic moieties to the brain. Direct targeting the brain via olfactory and trigeminal neural pathways by passing the BBB has gained an important consideration for delivery of wide range of therapeutics to brain. Intranasal route of transportation directly delivers the drugs to brain without systemic absorption, thus avoiding the side effects and enhancing the efficacy of neurotherapeutics. Over the last several decades, different drug delivery systems (DDSs) have been studied for targeting the brain by the nasal route. Novel DDSs such as nanoparticles (NPs), liposomes and polymeric micelles have gained potential as useful tools for targeting the brain without toxicity in nasal mucosa and central nervous system (CNS). Complex geometry of the nasal cavity presented a big challenge to effective delivery of drugs beyond the nasal valve. Recently, pharmaceutical firms utilized latest and emerging nasal drug delivery technologies to overcome these barriers. This review aims to describe the latest development of brain targeted DDSs via nasal administration.

Chemical compounds studied in this article: Carbopol 934p (PubChem CID: 6581)
Carboxy methylcellulose (PubChem CID: 24748)
Penetratin (PubChem CID: 101111470)
Poly lactic-*co*-glycolic acid (PubChem CID: 23111554)
Tween 80 (PubChem CID: 5284448)

1. Introduction

Despite of the tremendous advancement in drug delivery systems (DDSs) for treatment of central nervous system disorders like schizophrenia, migraine, Parkinson's, Alzheimer's disease and brain tumors, still there is need of novel brain targeted DDSs. The major hurdle for targeting the drug to brain is the presence of BBB. BBB is the delicate network of blood vessels having tightly packed endothelial cells which separates the brain from circulatory system. It protects brain from entry of harmful substances such as toxin and bacteria. Hydrophilic substances, charged molecules, proteins and peptides are unable to cross this barrier, whereas lipophillic drugs such as antidepressants, anxiolytics and many hormones can easily cross the endothelial cells [1]. Patients suffering from neurological disorders required chronic dosing, leading to side effects in non targeted organs. It is considered that majority of drugs which are useful to treat the neurological disorders have lost their potential due to the BBB, resulting in limited treatment options for the patients suffering from neurodegenerative diseases and brain cancer [2]. Therefore, non-invasive transport of drug to brain is highly needed for neurological disorders and brain tumors requiring chronic therapy. Olfactory pathway is a reliable alternative to achieve desire therapeutic effects at lower doses for treating chronic diseases while minimizing the side effects. Transmucosal delivery of drug through olfactory or trigeminal pathway to brain by passing the BBB is referred as the direct IN drug transportation to brain. This is the only route through which brain is in connection with the outside environment [3]. This neural connection has gained attention for delivery of wide variety of drug molecules by the formulations ranging from small molecules to large molecules such as nucleotides, peptides and proteins to brain by preventing the enzymatic degradation and enhancing the pharmacological effects without systemic absorption and toxicity to the major peripheral organs. In animal and human studies, it was investigated that different DDSs by improving the nasal permeability, increasing mucoadhesion, providing constant or controlled release of drug or increasing deposition at olfactory epithelium resulted in successful delivery of drug from direct nose to brain [4,5].

This review highlights literatures regarding pathways and mechanisms of therapeutic agents transporting across nasal mucosa and latest developments on novel DDSs using various formulation strategies to improve the IN drug delivery to brain. Colloidal carriers such as various types of nanocarriers (NPs, micelles, nanogels, nanoemulsions and liposomes) and microspheres as potential DDSs to brain are main

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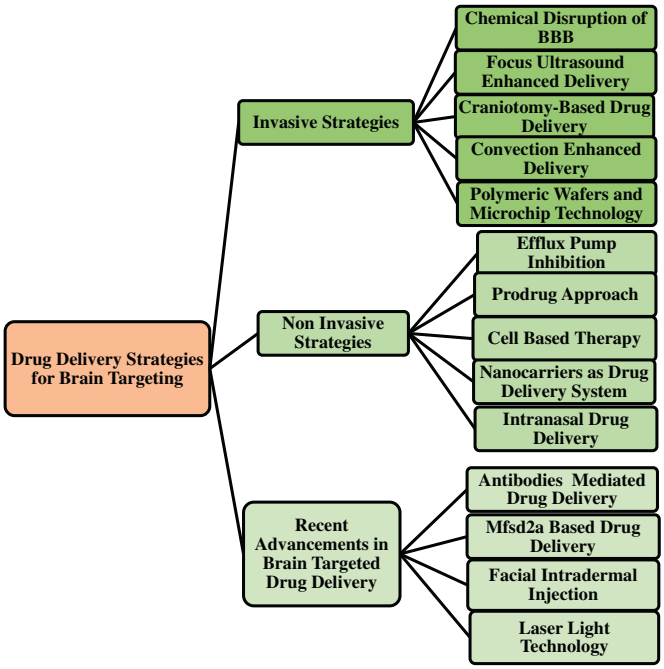

Fig. 1. Diagrametic presentation of drug delivery strategies for brain targeting.

focus of discussion. Patented technology based drug delivery devices for efficient nasal delivery of drugs are highlighted in this review. Moreover, limitations as well as future prospects of such brain targeted DDSs are also discussed in details.

2. Drug delivery strategies for brain targeting

Various drug delivery strategies to disrupt or overcome the BBB and potentiate the transport of drug molecules across this barrier to the CNS have been studied. These strategies are divided into three main categories; invasive and non invasive strategies and recent techniques for BBB disruption (Fig. 1).

2.1. Invasive strategies

2.1.1. Chemical disruption of BBB

Numerous invasive techniques are used to disrupt the BBB and enhance the delivery of drug to brain. Osmotic disruption of BBB is one of the invasive techniques involving temporarily shrinkage of endothelial cells, opening of tight junctions and leakage of drug to the CNS [6–8]. On injecting intracarotid hypotonic solution of mannitol, tight junctions were opened and subsequently promoted the delivery of chemotherapeutic agents to the brain. Osmotic disruption enhanced 2.5–7.6 fold transport of methotrexate, aminoisobutyric acid and dextran 70 to CNS [9]. This technique is less specific and inefficient and major drawbacks are transport of plasma protein to CNS, disturbed glucose uptake, microembolism, neurotoxicity of cerebral tissues, altered brain functions and technicality related issues.

Vasoactive agents such as bradykinin and histamine disturb the BBB and improve the transportation of drugs to CNS [10–12]. Purpose mechanisms involved in BBB opening effects of bradykinin are the activation of B2 receptors, leakage of endothelial cells based on modulation of caveolin-1 and caveolin-2 [13] and permeability enhancement of brain tumor microvessels via (KATP) channels [14]. In preliminary clinical trials, intra arterial infusion of RMP-7, agonist of bradykinin, resulted in 2.7 fold enhanced transport of carboplatin [15] but phase II and III clinical trials had shown inefficiency of RMP-7 in the treatment of glioma [16,17]. The Transient effect and unevenly distribution of receptors in the brain led to the poor distribution of chemotherapeutic agents in brain [18]. Efficiency of vasoactive agents could be maintained by conjugating onto the surface of NPs. A study has shown that coupling of methylmethacrylate-sulfopropylmethacrylate (MMA-SPM) NPs with RMP-7 resulted in successful delivery of antiretroviral drug across BBB. This strategy of combining liposomes or NPs encapsulating drugs with hyperosmotic agents has shown positive results in improving drug delivery to brain and reducing systemic side effects [19]. Liposomes grafted with peptidase inhibitors [20], bradykinin and etoposide [21] promoted the transport of encapsulated drugs across BBB.

2.1.2. Focus ultrasound enhanced delivery

The use of ultrasound waves to reversibly and transiently open the BBB is another versatile approach for enhancing of drug transportation to the CNS [22]. Ultrasound based drug delivery utilized microbubbles (MBs) as a contrast agent [23,24]. These bubbles were administered systemically and worked on acoustic energy principle to exert pressure on endothelial cells and open the tight junctions, resulted in increased permeability of BBB and improved delivery of drug to the brain [25]. MBs have diameter of 1–10 μm and are made of semi rigid lipid and albumin shells encapsulated with perfluorocarbon [26]. These MBs operate in collaboration with low intensity Focus Ultrasound (FUS) and this combined system is called MB facilitated FUS. MB-FUS system decreases the acoustic energy requirement, focusing the acoustic energy within blood vessels. Different antitumor agents such as trastuzumab [27], temozolomide [28], methotrexate [29], neucleotides i.e. siRNA [30] and stem cells [31] have been successfully delivered with the help of FUS. FUS-MB system is effectively used with other DDSs for brain targeted delivery. This system could be utilized in combination with PEGylated NPs to disrupt the BBB for enhanced delivery, target the cancerous cell and increase penetration [32]. FUS technique coupled with liposomes had shown optimum effects of doxorubicin in rat glioma [33]. FUS grafted gold NPs guided through MRI were delivered to brain tumor model. FUS system could be helpful for gene therapy of brain tumor [34]. Successful delivery of NPs encapsulating reporter gene combined with MRI guided FUS to transfect the brain, is the clue for future prospects of this technology for gene therapy [35].

High-Intensity Focused Ultrasound (HIFU) is effectively applied for reversible disturbance of BBB and promotion of drug distribution to the brain in a précised and controlled way without toxicity to brain parenchyma tissues. This technique is valuable for tumor targeted delivery of drugs, genes and antibodies [36–38]. Interstitial fluid pressure limited the distribution of NPs to the tumor. HFU increased the permeability of endothelial cells and NPs were moved from leaky endothelial cells to the tumor microenvironment resulting in improved distribution of anticancer agents to the tumor targeted area.

2.1.3. Craniotomy-based drug delivery

Craniotomy-based drug delivery is the direct way of targeting the specific part of the brain without exposure to peripheral organs via Intracerebral or intraventricular injection. In intraventricular delivery, drug reservoir implanted in the scalp provided the controlled release of a drug and is connected to the ventricles in the brain through catheter [39,40]. Higher concentration of drugs is achieved without distribution to the interstitial fluid of brain. Intraventricular system directly delivers the drug to the ventricles and subarachnoidal part of the brain and is suitable for therapy of meningioma and metastatic cells of CSF [41]. Intracerebral system directly injects or infuses the drug into brain parenchyma through catheter [42] and controlled devices maintain the delivery [43]. This system depends on the diffusion mechanism and provides slow distribution of drugs within the brain, as diffusion decreases with the increase of distance. Hence, intracerebral delivery requires large doses of a drug to achieve desired therapeutic response [44].

2.1.4. Convection-enhanced delivery (CED)

Convection-enhanced delivery (CED) overcomes the disadvantages

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