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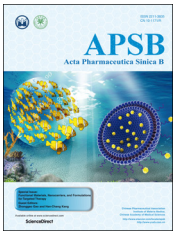

REVIEW

Progress and perspectives on targeting nanoparticles for brain drug delivery

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Abstract Due to the ability of the blood–brain barrier (BBB) to prevent the entry of drugs into the brain, it is a challenge to treat central nervous system disorders pharmacologically. The development of nanotechnology provides potential to overcome this problem. In this review, the barriers to brain-targeted drug delivery are reviewed, including the BBB, blood–brain tumor barrier (BBTB), and nose-to-brain barrier. Delivery strategies are focused on overcoming the BBB, directly targeting diseased cells in the brain, and dual-targeted delivery. The major concerns and perspectives on constructing brain-targeted delivery systems are discussed.

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1. Introduction

In the past two decades, nanotechnology has been developing quickly and is widely used in disease diagnosis and treatment. Various kinds of nanoparticle (NP)-based drug delivery systems have been constructed using emerging novel nanomaterials. These NPs include liposomes, dendrimers, micelles, polymer nanoparticles and inorganic nanoparticles[1], which can carry therapeutic drugs or imaging probes and deliver them to target site. NPs provide many benefits, including improving the solubility, protecting cargoes from digestion by enzymes, elevating targeting efficiency and enhancing cellular internalization. Therefore, NPs have gained increasing attention in the field of medicine and biology.

Currently, disorders in central nervous system (CNS) with significant consequences and attention include Alzheimer's disease (AD), Parkinson's disease (PD) and brain tumors[2]. However, the diagnosis and treatment of CNS disorders is far from impressive, owing to the restriction by blood–brain barrier (BBB) of drug transport into the brain[3], with almost 100% of the macromolecular drugs and over 98% of the small-molecule drug candidates unable to enter the brain[4]. Other than nutrients, only small lipophilic molecules (<500 Da) can effectively cross the BBB and reach an efficacious brain concentration[5]. To conquer the BBB and deliver diagnostic and therapeutic drugs to the brain, various kinds of strategies have been developed using NPs as carriers.

In this review, the biology of the BBB and other neural barriers that restrict brain-targeted drug delivery are described. Recent advances in brain-targeted drug delivery are discussed which focus on NPs-based strategies. Lastly, the shortage of recent studies and potential future approaches are discussed.

2. Physical barriers in brain targeting

2.1. BBB

The BBB is the most important barrier in brain-targeted delivery. It was first discovered by Ehrlich in 1885, who found that intravenously injected dye could stain most organs except the brain[6,7]. The BBB is composed of several kinds of cells, including brain capillary endothelial cells (BCECs), pericytes, astrocytes and neuronal cells[8,9]. BCECs are the main component of BBB. Different from peripheral endothelial cells, BCECs possess several specific characteristics[9]. Most importantly, the continuous tight junctions between the BCECs prevent paracellular transport of compounds from blood to brain[9]. These tight junctions also result in extremely high transendothelial electrical resistance (TEER) between the blood and brain and the passive diffusion of compounds is considerably restricted[8,10]. Despite the restriction on passive diffusion and paracellular transport from blood to brain, there are various kinds of transporters or carriers that can mediate the uptake to brain or extrusion from brain[9,11,12] of various substances, as discussed in Section 3.

2.2. Blood–brain tumor barrier (BBTB)

In brain tumors, especially in advanced brain tumors, the BBB is compromised in the core but is integral in the surrounding area[13,14]. For example, the distribution of erlotinib in the U87 tumor core is 4.69-fold higher than that in the brain around the tumor core[15]. However, drug distribution to brain tumor is more restricted than is found with peripheral tumors. In a metastatic breast tumor-bearing mouse model, the lapatinib concentration in lung metastasis tissue is 5.15-fold higher than that in brain metastasis[16]. It is assumed that the BBTB restricted the distribution of drugs from blood to brain tumor[2,17,18]. Compared with blood tumor barriers in peripheral tumors, the BBTB exhibits a smaller pore size and expresses a higher level of drug efflux pumps, such as P-glycoprotein, multidrug-resistance-associated proteins, and breast-cancer resistance protein[19–23].

2.3. Nose to brain barrier

The anatomy, physiology and brain delivery route of the nasal cavity have been well reviewed[24,25]. Basically, two parts of the nasal cavity, the respiratory region and the olfactory region, are responsible for drug absorption into brain or blood. Through the respiratory region mucosa some compounds can enter the systemic circulatory system and subsequently cross the BBB to brain, while some can be directly transported to brain *via* the trigeminal nerve pathway or lamina propria adsorption from perivascular and lymphatic spaces[25]. Through the olfactory mucosa compounds can be transported into the olfactory bulbs and then into cerebrospinal fluid through lamina propria absorption, olfactory nerves, lymphatic and perivascular spaces, and the trigeminal nerve pathway. Among these pathways, the olfactory mucosa pathway is the most rapid, and thus it is the main pathway that mediates drug delivery from the nasal cavity to the brain. Nonetheless, the volume that can be intranasally administered is very small (25–200 μL), which can limit the drug dose and the concentration of drug transported into brain. The nasal cilial clearance further diminishes the absorption time of drug in the nasal cavity and drug metabolism and secretion can also inhibit the drug transfer into the brain[25].

3. Strategies to overcome the BBB

To deliver drugs to the brain, the BBB is the first barrier. Researchers have developed various kinds of strategies to overcome or bypass the BBB, including penetrating through BBB by cellular internalization, opening BBB and intranasal delivery[2].

3.1. Penetrating through BBB

Although the BBB is intact, there are many receptors and carriers that are overexpressed on the BBB (Table 1)[26–35], which can mediate the transport of specific ligands and their cargoes. Additionally, the membrane of the BBB is negatively-charged and shows high affinity with positively-charged compounds, which could also trigger the internalization by cells. Thus these kinds of ligands could mediate the penetration of NPs through the BBB.

3.1.1. Receptor-mediated transportation

On the BBB many receptors are overexpressed, including the transferrin (Tf) receptor, insulin receptor, low-density lipoprotein receptor–related protein, nicotinic acetylcholine receptor, insulin-like growth factor receptor, diphtheria toxin receptor, scavenger receptor call B type, leptin receptor and the neonatal Fc receptor[12,30]. These receptors can specifically bind with corresponding ligands and trigger internalization into cells. Thus, the corresponding ligands could be functionalized onto NPs to mediate their transport through BBB. Due to the specificity of the interaction between receptors and ligands, the receptor-mediated transport has