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Review

Non-invasive approaches for drug delivery to the brain based on the receptor mediated transport

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ABSTRACT

The blood brain barrier (BBB) is a physical and biochemical barrier that prevents entry of toxic compounds into brain for preserving homeostasis. However, the BBB also strictly limits influx of most therapeutic agents into the brain. One promising method for overcoming this problem to deliver drugs is receptor mediated transport (RMT) system, which employs the vesicular trafficking machinery to transport substrates across the BBB endothelium in a noninvasive manner. The conjugates of drug or drug-loaded vector linked with appropriate ligands specifically binds to the endogenous targeting receptor on the surface of the endothelial cells. Then drugs could enter the cell body by means of transcytosis and eventual releasing into the brain parenchyma. Over the past 20 years, there have been significant developments of RMT targeting strategies. Here, we will review the recent advance of various promising RMT systems and discuss the capability of these approaches for drug delivery to the brain.

Contents

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1. Introduction

Brain diseases such as Parkinson disease (PD), Alzheimer's disease (AD) and brain tumor are serious threats to human health. Many drugs with considerable promises have been developed to treat brain disorders every year. However, the blood brain barrier (BBB), heavily restricts the passage of therapeutic agents from the blood to the brain. The BBB regulates ionic and molecular traffic, which results in essential blocking 100% of large molecule drugs and more than 98% of small molecule drugs [1]. As shown in Fig. 1, the BBB is composed of brain capillary endothelial cells (BCECs), tight junction (TJ), basal lamina, astrocyte end-feet and pericytes [2]. The BCECs are tightly closed by the TJ and covered by basal lamina. In addition, the pericytes partially envelope the basal lamina, and the astrocyte end-feet almost 100% encircling of the microvessel wall.

The BCECs, differing from other vessel cell membranes, consist of a lipid bilayer which is lack of fenestrations and pinocytotic vesicles [3]. The high concentration of sterols and lipids, up to 20% and 50% respectively [4], might increase the packing density and decrease the permeability of brain endothelium. In addition, the substance traffic is further limited by the catabolic enzymes and efflux transporter such as P-glycoprotein (Pgp), multidrug resistance related proteins (MRPs) and breast cancer resistance protein (BCRP) [5]. Moreover, TJ seals the paracellular cleft of epithelial cells to form a 'physical' barrier. Occludin, claudin, junction adhesion molecules and a series of cytoplasmic accessory proteins represent the major integral components of bicellular TJ [6]. The basal lamina is approximately 30–40 nm thick, and located between the endothelial cells and astrocyte, consisting of laminin, fibronectin, tenascin, collagen, and proteoglycan [7]. The pericytes cover about 20%–30% of the outer microvascular circumference. The proliferation of brain blood endothelium might be influenced by the pericytes via selective inhibition of endothelial cell growth [8]. Astrocytes enclose more than 99% of the basal capillary membrane and play an indispensable role in the induction and maintenance of BBB integrity [7]. The basal lamina, pericytes, and astrocytes as a physical barrier might limit the transport of substances into brain tissues.

Many drugs cannot penetrate BBB and present therapeutic effect due to the specific structure and function of the BBB. Therefore, more promising strategies have been studied for efficient drug delivery to the brain. At present, these methods can be classified into two types, invasive and noninvasive approaches.

1.1. Invasive approaches

Invasive approaches, which allows the direct transfer of the drug into the lesions on the brain, include CED (convection enhanced delivery) [9–13], ICV (intracerebroventricular) [14], intracerebral injection and disruption of the BBB using osmotic disruption, ultrasound [15,16], and bradykinin analogs. Although invasive approaches could deliver drugs into the brain, these methods present some risks, such as lack of targeting, traumatic and some of surgical complications. In addition, because these methods require sophisticated device and professional technique, the widespread application of these methods is limited.

1.2. Non-invasive approaches

The noninvasive approaches mainly include carrier mediated transport (CMT), adsorption mediated transport (AMT), receptor mediated transport (RMT) and so on. The schematic of presentation various mediated transport systems is shown in Fig. 2. The CMT mechanism can mediate the entry of major nutrients such as glucose, amino acid, monocarboxylic acid, vitamin, and nucleotides into the brain. Some small hydrophilic molecules might across the BBB by use of CMT systems via conjugate with the natural CMT ligands, such as amino acid transporter, hexose transporter and monocarboxylic acid transporter [17]. AMT is a vesicle transport system. The cationic drugs bind to the negatively charged domains of luminal surface via electrostatic attraction, and further trigger the endocytosis of intracellular vesicles containing the drug. Then, the drug is transported by vesicles within the endothelial cells and eventually cross the abluminal surface into the brain parenchyma [18]. In addition, unlike the delivery mechanism of intravenous administration, the intranasal administration is also an effective non-invasive approach which allows some proteins, peptides and other drugs to bypass the BBB and access the CNS regions. Many drugs can be transported into the brain via olfactory nerves to the olfactory bulbs and rostral brain regions or via trigeminal nerves to the brainstem and spinal cord region [19–21].

RMT involves the vesicular trafficking system of the brain endothelium. A circulating ligand binds to a cognate transmembrane receptor, such as transferrin receptor or insulin receptor, which is expressed on the apical plasma membrane (blood side) of the endothelial cell. The process of endocytosis takes place and membrane invagination leads to the formation vesicle that contains receptor-ligand conjugates. Subsequently, the conjugates are dissociated, and the vesicles of receptor return to the apical. However, the vesicles of ligand can be trafficked to the basolateral, where the ligand fuse with the membrane and are released into the brain parenchyma [22,23].

In recent years, the RMT-based drug delivery system becomes a hot research topic for overcoming the BBB. A large number of RMT approaches have been developed. In this article, we will review the RMT systems that have been used for brain disorders and discuss the efficiency of each RMT systems.

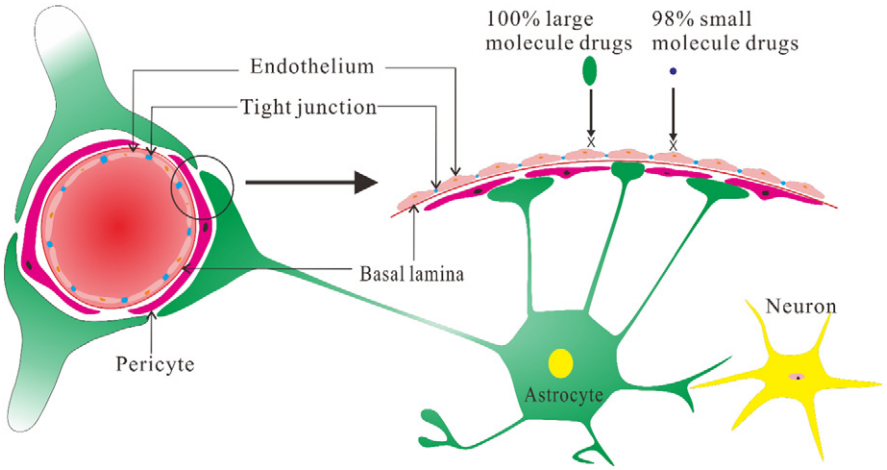

Fig. 1. The diagrammatic sketch of the BBB structure.