Blood–Brain Barrier

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The blood–brain barrier (BBB) is a natural obstacle for drug delivery into the human brain, hindering treatment of central nervous system (CNS) disorders such as acute ischemic stroke, brain tumors, and human immunodeficiency virus (HIV)-1-associated neurocognitive disorders.

Keywords: blood–brain barrier (BBB) ; PLGA ; cGMP

1. Blood–Brain Barrier (BBB) and Drug Delivery

Compared with other therapeutic areas, drug development is more challenging for brain diseases such as brain cancers, Alzheimer's diseases (AD), acute ischemic stroke, and human immunodeficiency virus (HIV)-1-associated neurocognitive disorders (HAND) [1][2][3][4]. Many systemically administered drug products cannot pass the BBB [5]. The BBB restricts the entry of compounds into the central nervous system (CNS) through the presence of brain microvascular endothelial cells, pericytes, perivascular astrocytes, and tight junctions. In addition, the presence of efflux transporters at the BBB has been recognized as a key element to poor drug penetration [6][7]. ATP-binding cassette (ABC) membrane-associated transporters, such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated protein (MRP1) show significant expressions at the BBB, protecting the brain from potential harmful endogenous and exogenous substances [6][7]. As a result, the BBB only selectively transports molecules such as certain amino acids, sugars, and gaseous molecules (e.g., oxygen and carbon dioxide) into the brain [8]. For example, antiretroviral drugs (ARVs) have shown to be effective in managing HIV-1 [9]. However, due to the inability of ARVs to cross the BBB, they are not highly recommended clinically for the treatment of HAND.

2. Strategies to Cross BBB

Several strategies have been used to improve drug delivery to the brain. Efforts have been made for the development of inhibitors for ABC transporters due to their high expressions on the BBB [2][10][11]. Studies showed that blocking ABC transporters may significantly improve drug penetrations across the BBB. However, this method has not been used clinically due to the wide distribution of ABC transporters throughout the body, the potential toxicity of inhibitors, and unexpected drug–drug interactions [10]. Another approach is the "BBB opening" approach. Opening the BBB can be achieved by using a hyperosmotic solution to shrink the endothelial cells or using certain cytotoxic agents to disrupt the BBB tight junctions [10][11]. However, opening the tight junctions of the BBB is risky clinically because it may also allow the entry of harmful components into the brain and cause side-effects such as seizures and other long-term neurological complications [10]. Moreover, the development of prodrugs to increase their capacity to penetrate the BBB is another potential delivery approach [10]. Prodrugs can be synthesized with sufficient lipophilicity to facilitate the crossing of the endothelial cell membrane and release the parent ARVs into the brain. However, developing prodrugs as a delivery strategy needs a full evaluation of toxicity, cost, and efficacy, as prodrugs are considered to be a separate chemical entity.

A nanoparticle (NP)-based drug delivery system is considered a promising option to improve drug delivery to the brain [3]. NP-based formulations are usually a colloidal system made of polymers, lipids, or other large macromolecules such as albumin. A therapeutic agent may be released through diffusion or erosion of the matrix [12]. The NP-based delivery system can cross the BBB through membrane transcytosis, bypass efflux transporters, and effectively deliver the therapeutic molecule to the CNS [3]. NPs that have been studied for brain delivery include polymeric NPs such as poly(d,l-lactide-co-glycolide) (PLGA) [13][14] and poly(butyl-cyanoacrylate) (PBCA) NPs [15][16], magnetic NPs (MNPs) composed of an iron oxide core [16], lipid-based nanoformulations such as solid lipid nanoparticles (SLN) and liposomes [10][16], and polymeric micelles-based nanoformulations such as Pluronic micelles [10]. Extracellular vesicles (EVs), liposome-like natural carriers, have drawn attention for delivering drugs into the brain as a potential alternative to NPs [17][18][19].

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