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Drug Delivery Through Blood Brain Barrier: Taming the Bottleneck in CNS Therapeutics

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Abstract

Although many agents have therapeutic potentials for Central Nervous System (CNS) diseases, few of these agents have been clinically used because of the brain barriers. Physiological barriers like the blood-brain barrier and blood-cerebrospinal fluid barrier as well as various efflux transporter proteins make the entry of drugs into the central nervous system very difficult. Different strategies for efficient CNS delivery have been studied. This review presents the current approaches to facilitate penetration across these barriers for enhanced drug delivery to the CNS.

Keywords: Blood Brain Barrier, CNS Drug Delivery

1. Introduction

The Blood-Brain Barrier (BBB) is a complex structure that stabilizes the neuronal microenvironment. It is formed by tight junctions between neighboring endothelial cells that allows a highly restricted passage of the components from the blood through it.[1] The endothelium thus transports certain substrates but excludes others as this continuous barrier cannot be bypassed extra-cellularly.[2] Efflux transporters such as P-glycoprotein also functions in the same manner. It is encoded by the Multidrug Resistance Gene (MDR1) and is present in high concentration on the apical surface of these endothelial cells in brain capillaries. Though P-gp protects the brain from exposure to a number of pharmacologically active hydrophobic agents, it also restricts the entry of a variety of therapeutic agents used in the treatment of various CNS diseases like neurodegenerative disorders, brain tumors, epilepsy, HIV encephalopathy, cerebrovascular disease, including other brain pathologies. These agents include epipodophyllotoxins, Vinca alkaloids, anthracyclines, cyclosporine A, digoxin, and various HIV protease inhibitors. P-gp can be inhibited by various reversal agents including calcium channel blockers such as verapamil, calmodulin antagonists such as phenothiazines, quinolines, immunosuppressive agents such as cyclosporin A, antibiotics such as cefoperazone, rifampicin, steroid and hormonal analogs, reserpine, and surfactants. However, doses of most of these agents required for this inhibition elicit significant toxicity. Since the existing conventional CNS drug delivery systems have proven inefficient, research has aggressively focused on developing newer strategies that could deliver drug molecules to the brain more effectively. [3,4] (figure 1).

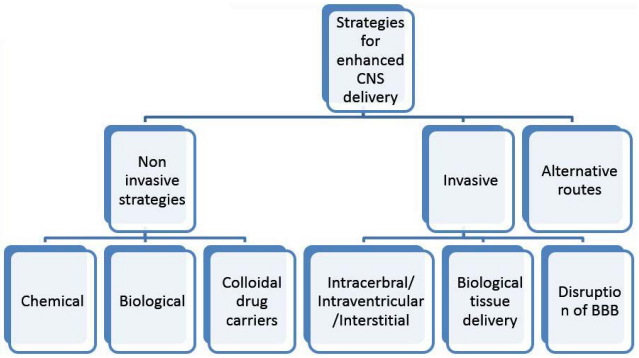

Figure 1. Strategies for enhanced CNS drug delivery.

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2. Non-invasive Strategies

A. Chemical Methods

Lipophilic analogs: Lipophilicity favors drug penetration through the BBB, hence the small hydrophobic analogs tend to penetrate the BBB more readily than their hydrophilic counterparts.[5] However lipidation of a drug markedly changes its pharmacokinetic parameters like volume of distribution and rate of enzymatic oxidative metabolism. These limitations can partially offset the advantages offered by this method.[6]

Prodrugs: Prodrugs, on administration, undergo chemical conversion to become an active pharmacological agent. This method is used to make a drug more lipophilic with chemical modification. This has been successfully tried in case of morphine which cannot enter the CNS by itself but does so easily after acetylation of both hydroxyl groups. However, some prodrug molecules have the potential to alter the original tissue distribution, efficacy and toxicity of the parent drug.[6]

Chemical drug delivery systems (CDS): This is a retro metabolic drug design approach where the drug is passed through the BBB as its lipophilic precursor. One or more chemical modifications of a drug form an inactive chemical derivative that undergoes multi-step enzymatic or chemical transformations to provide site specific or site enhanced delivery. Two bio-removable moieties are attached: a targeted (T) responsible for targeting a specific site and lock-in; and modifier functions (F1-Fn) that prevent unwanted metabolic conversions. This has been successful using 1,4-dihydrotrigonelline-Trigonelline system. Here the lipophilic 1,4-dihydro form (T) is converted to the hydrophilic quaternary form (T+) in-vivo which gets locked in the brain, but easily eliminated from the body due to enhanced water solubility. These systems have been tried in case of anti-infective agents, steroid hormones, anti-retroviral agents and anticancer agents.[5]

Molecular packaging: This has been done to achieve brain delivery of peptides which do not enter the CNS because of their hydrophilic character and the presence of peptidases in the lipid BBB. Here, a bulky molecule contains the peptide unit along with the groups that direct BBB penetration and prevent recognition by peptidases. This strategy has been used to deliver an opioid peptide (enkephalin) and a Thyrotropin-Releasing Hormone (TRH) analogue to the CNS.[5,7]

B. Biological Methods

Carrier-Mediated Drug Delivery: This method makes use of facilitated influx transporters of brain capillaries. Including carriers for glucose (GLUT1), Monocarboxylic Acids (MCT1), Large Neutral Amino Acids (LAT1), Cationic Amino Acids (CAT1), and nucleosides (ENT 1-2, CNT1-2) and choline. Various polar therapeutic drugs like L-DOPA, α-methyl-DOPA, gabapentin, and melphalan pass BBB via carrier-mediated transport. LAT1 mediated transport has been utilized for transport of two anticancer alkylating drugs.[8]

Receptor/Vector Mediated Drug Delivery of Chimeric Peptides: This method couples a non-transportable peptide pharmaceutical to a transportable peptide or protein, which undergoes receptor-mediated transcytosis through the BBB. The murine OX26 monoclonal antibody to the rat transferrin receptor undergoes receptor-mediated transport through the BBB. This technology has been used to transport Vasoactive Intestinal Peptide analog (VIPa) (nontrans portable pharmaceutical) by forming a chimeric peptide consisting of VIPa and a covalent conjugate of mouse Mab OX26 and avidin vector.[5,6,9]

Cell-Penetrating Peptide (CPP)-Mediated Drug Delivery: CPPs are the positively charged peptides containing a sequence of highly basic amino acids that permeates the cell membrane via a receptor and transporter independent mechanism and also transport the molecules that are tagged to them across the cell membrane. HIV-1 (human immunodeficiency virus [HIV] type 1] Trans-Activating Transcriptional activator (TAT) peptide is the most widely studied peptide. It destabilizes the phospholipid bilayer by interacting with negatively charged phospholipids in plasma membrane and forms an inverted micelle to pass through the membrane.[6]

C. Colloidal Drug Carriers

The extensively studied colloidal drug carriers are polymeric Nanoparticles (NPs), solid lipid nanoparticles, micelles, liposomes, emulsions, nanogels, nanosuspensions and dendrimers. Various in vitro and in vivo BBB models have effectively transported these nanomedicines by endocytosis and transcytosis. This strategy can be used for management of CNS conditions such as brain tumors, HIV encephalop-

athy, Alzheimer's disease and acute ischemic stroke.[10] NPs are overcoated with polysorbates, especially polysorbate 80 which adsorbs apolipoprotein E from blood plasma onto the NP surface. NPs now mimic Low Density Lipoprotein (LDL) particles and interact with the LDL receptor which leads to their uptake by the endothelial cells. The drug is then released in these cells and diffuses into the brain interior or the particles may be transcytoses.[11]

3. Invasive Strategies

The delivery of highly potent drugs like anticancer drugs to the CNS by systemic routes is liable to cause serious side effects. To limit the occurrence of these effects, these drugs can be administered directly into the brain tissue or by disruption of the BBB.[6]

A. Intracerebral Implants/ Intraventricular/ Intrathecal/ Interstitial Delivery

These strategies directly overcome the barriers to tumor drug delivery and are hence considered mainly for the management of primary brain tumors. But these have certain disadvantages including CNS infection, catheter obstruction, and inadequate drug distribution.[12]

B. Biological Tissue Delivery

This strategy employs implanting a tissue that secretes the desired therapeutic agent naturally into the brain. This has been widely applied in the management of Parkinson's disease where reconstitution of the normal nigrostriatal pathway is attempted by neural transplantation so as to restore striatal dopamine. Poor graft survival is one of the most difficult issues with this approach which can be partially overcome by trophic factors such as Brain-Derived Neurotrophic Factor (BDNF), Epidermal Growth Factor (EGF).[12]

C. BBB Disruption (BBBD) Strategies

Convection-Enhanced Delivery (CED): This involves the delivery of drugs through the catheters placed stereo tactically into the brain through cranial burr holes using micro infusion pump.[6]

Osmotic BBBD Strategy: This strategy mostly employs the use of hyperosmolar mannitol solution which disrupts the endothelial tight junctions and causes the shrinkage of cerebrovascular endothelial cells, thus increasing the BBB permeability.[6,13]

Biochemical BBBD Strategy: Here the capillary permeability is increased using some vasoactive compounds, including leukotrienes, bradykinin, and histamine.[14]

Ultrasound (US)-Mediated BBBD Strategy: US induce mild hyperthermia which can increase delivery of drug to the CNS.[15]

4. Alternative Routes for CNS Drug Delivery

These include olfactory and trigeminal pathways to the CNS and iontophoretic delivery to deliver ionized molecules across the BBB by using an externally applied electric current.[6,16]

5. References

1. Schlosshauer B. The blood-brain barrier: morphology, molecules, and neurothelin. Bioassays. 1993; 15:341–6. https://doi.org/10.1002/bies.950150508 PMid:8102053
2. Brightman MW, Zis K, Anders J. Morphology of cerebral endothelium and astrocytes as determinants of the neuronal microenvironment. In: Hossmann KA, Klatzo I, editors. Cerebrovascular transport mechanisms. Acta Neuropathologica Supplementum. Berlin: Springer; 1983. p. 21–33. https://doi.org/10.1007/978-3-642-68970-3_2 PMid:6346778
3. Martin B, Robert L, Henry B, Mathiowitz E. Encyclopedia of controlled drug delivery, Vol. l, New York: John Wiley and Sons Inc; l999. p. 184-210.
4. Pankajavalli R. The role of P-glycoprotein in the blood-brain barrier. Einstein Quart J Biol Med. 2003; 19:160–5.
5. Dwibhashyam VS, Nagappa AN. Strategies for enhanced drug delivery to the central nervous system. IJPS. 2008; 70(2):145–53. https://doi.org/10.4103/0250-474X.41446 PMid:20046703 PMCid:PMC2792490
6. Lu C-T, Zhao Y-Z, Wong HL, Cai J, Peng L, Tian X-Q. Current approaches to enhance CNS delivery of drugs across the brain barriers. Int. J Nanomedicine. 2014; 9:2241–57. https://doi.org/10.2147/IJN.S61288 PMid:24872687 PMCid:PMC4026551
7. Bodor N. A strategy for delivering peptides into the central nervous system by sequential metabolism. Science. l992; 257:1698–700.

8. Smith QR. Carrier-mediated transport to enhance drug delivery to brain. International Congress Series. 2005; 1277:63–74. https://doi.org/10.1016/j.ics.2005.02.012
9. Kang YS, Bickel U, Pardridge WM. Pharmacokinetics and saturable blood-brain barrier transport of biotin bound to a conjugate of avidin and a monoclonal antibody to the transferrin receptor. Drug Metab Dispos. 1994; 22(1):99–105.PMid:8149897
10. Wong HL, Wu XY, Bendayan R. Nanotechnological advances for the delivery of CNS therapeutics. Adv Drug Deliv Rev. 2012; 64:686–700. https://doi.org/10.1016/j.addr.2011.10.007 PMid:22100125
11. Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev. 2001; 47:65–81. https://doi.org/10.1016/S0169-409X(00)00122-8
12. Scheld WM. Drug delivery to the central nervous system: general principles and relevance to therapy for infections of the central nervous system. Rev Infect Dis. 1989; 11 Suppl 7:S1669–90. https://doi.org/10.1093/clinids/11.Supplement_7.S1669 PMid:2690302
13. Rapoport SI, Robinson PJ. Tight-junctional modification as the basis of osmotic opening of the blood–brain barrier. Ann N Y Acad Sci. 1986; 481:250–67. https://doi.org/10.1111/j.1749-6632.1986.tb27155.x
14. Cloughesy TF, Black KL. Pharmacological blood–brain barrier modification for selective drug delivery. J Neurooncol. 1995; 26:125–32. https://doi.org/10.1007/BF01060218
15. Cho CW, Lin Y, Cobb WN. Ultrasound-induced mild hyperthermia as a novel approach to increase drug uptake in brain micro vessel endothelial cells. Pharm Res. 2002; 115:413–24.
16. Mathison S, Nagilla R, Kompella UB. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug Target. 1998; 5:415–41. https://doi.org/10.3109/10611869808997870 PMid:9783675

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