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CNS Delivery of Drugs: Challenges and Chances

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Drug delivery to the CNS is particularly a challenging task owing to triple hurdles: the blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier (B-CSFB) and the blood-tumor barrier (BTB). It is now well recognized that the BBB is a unique membranous barrier that tightly segregates the brain from the circulating blood [1]. The construction of the BBB impedes drug transport to the brain and spinal cord where the brain capillary endothelium lack fenestrations and are sealed with tight junctions. The tight junctions furnishes a very high trans-endothelial electrical resistance of >1500 Ωcm^2 compared to 3-30 Ωcm^2 of capillaries in other tissues. Hence it reduces the aqueous-based paracellular diffusion that is observed in other organs and presents a "passive" physical barrier. The BBB presents also an 'active' barrier that precludes drug access namely: the efflux pumps. Finally, the BBB has additional enzymatic aspects which serve to protect the brain. On the other side, the drug physicochemical properties rigorously affect drug permeation across the BBB. The "CNS-likeness" dictates that: the drug should have a smaller optimal range of molecular weight (<450), lipophilicity (CLogP<3), and hydrogen-bond donors (HBD<4) as well as hydrogen-bond acceptors (HBA<8) [2]. Drug permeation does not grant its uptake since it might be actively effluxed by ATP binding cassette (ABC) transport proteins, including P-glycoprotein (P-gp), Multidrug Resistance Protein-1 (MRP-1), and Breast Cancer Resistance Protein (BCRP) greatly expressed in the luminal membranes of the cerebral capillary endothelium [3]. In order to cross the blood–brain barrier, a drug substance can either cross paracellularly, transcellularly via diffusion through lipid bilayers, or transcellularly via membrane transport proteins [4]. The blood-cerebrospinal fluid barrier (B-CSFB) is yet another hurdle that vigilantly controls the access of molecules ferried by the blood to the interstitial fluid of the brain parenchyma and CSF owing to the choroid plexus and the arachnoid membrane. The former passively and actively regulate drug passage into CSF by virtue of its tight junctions and its active organic acid efflux transporters respectively while the latter is largely passively impermeable to hydrophilic substances. Scientists demonstrated that entry into the CSF does not guarantee a drug's penetration into the brain pointing at the existence of the so called CSF-brain barrier [5]. Finally, the blood-tumor barrier (BTB) resulting from alterations in cerebral microvasculature as a result of tumor makes it even more difficult for drugs to permeate than normal brain endothelium, leading to exceptionally low extra-tumoral interstitial drug concentrations and continuous growth of intracranial malignancies.

Conceivably, detailed investigation in the brain physiology in normal and diseased conditions, the understanding of uptake and efflux transport system, the pursuit of suitable methods to study and/or predict BBB permeation and the embed of this knowledge in development of delivery tactics that maximize drug access to the brain are the focus of rigorous research. In this context researchers have done vigorous efforts to characterize and predict BBB permeability. Importantly the prediction of drug permeation was integrated in the early phases of drug development. The in-vitro models that closely mimic the in-vivo system are highly warranted. A wide range of in silico models and in vitro permeability assays has been generated but with variable success [6]. The vitro blood–brain barrier models developed included endothelial cells isolated from bovine brain, astrocyte-conditioned media, co-cultures of endothelial and glial cells, and generation of blood–brain barrier cells from stem cells. However, most attempts have failed to reproduce the tightness of the capillary endothelial tissue. The high paracellular permeability of primary cultures was a major limitation and hence was substituted by human immortalized endothelial cells. A strong correlation between the in-vivo and in-vitro results was achieved by the astrocytes model , hence it was claimed as potential rapid evaluation of strategies for achieving drug targeting to the CNS or to understand the eventual central toxicity of systemic drug and to elucidate the molecular transport mechanism of drugs across the BBB. The in situ perfusion method is considered the most accurate method of determining the blood–brain barrier permeability of a drug substance. However, this method is costly and not suited for screening studies [6]. While in order to study the pharmacokinetics and pharmacodynamics of drugs in the CNS property various in-vivo and in-vitro techniques were presented. The in-vivo techniques include the brain uptake index (BUI), the brain efflux index (BEI), brain perfusion, the unit impulse response method and microdialysis [6].

Concerning the tactics employed in the CNS delivery of drugs, these generally belong to one of the following four categories: disrupting the BBB, drug modification, physiological approaches and the use of nanocarriers. Traditionally, the temporarily disruption of the BBB was used by infusing hyperosmolar mannitol solutions intra-arterially whereby the endothelial cells dehydrate and shrink with a consequential widening of the tight junctions or by co-administration of the bradykinin agonist RMP-7. The mechanical disruption of the BBB was also employed to provide high drug concentrations locally at the site of action, while minimizing the drug levels in the rest of the human body, resulting in reduced side effects. However, the risks of causing CNS infections and the rapid clearance from the brain tissues (short brain half-lives) are serious restrictions limiting the frequent use of these methods [7]. Drug modification by chemical prodrug formation to enhance its BBB permeation or by linking it to a carrier has been frequently employed as a non-invasive tactic for crossing the BBB [8]. While increased lipophilicity by prodrug or lipophilic analogue formation may improve diffusion across the BBB, it also tends to increase uptake into other tissues, enhance its oxidative metabolism by cytochrome P-450 and other enzymes and/or predispose it to the aggressive efflux by P-gp and other transporters [9]. The olfactory pathway has also gained appraisal as a noninvasive method of drug targeting to the brain due to the existence of direct

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nose-brain transport through the olfactory mucosa, at the roof of the nasal cavity, and along the olfactory sensory neurons to yield significant concentrations in the CSF and olfactory bulb. In this context, investigators explored this pathway for treatment of Alzeheimer's disease and other neurodegenerative diseases with occasional success [10]. Recently, Shingaki and colleagues [11] were successful is utilizing the mainstay anticancer drug- methotrexate (MTX) -as nasal rather than injected MTX for brain tumor. They compared the concentration of MTX in the plasma and the CSF after intraperitoneal (IP) and intranasal (IN) administrations and noted significant direct transport of MTX from nasal cavity both to the CSF and to the brain. Moreover, IN MTX chemotherapy significantly reduced the tumor weight in rats as compared to nontreatment control and IP group. However, research in this area is highly demanding the invention of novel devices for targeted delivery to olfactory region of the nasal mucosa.

Drugs can be also modified to take advantage of endogenous BBB nutrient transport systems or by conjugation to ligands that recognize receptors expressed at the BBB [8]. Of the physiological approaches employed, conjugation of a drug with antibodies, sugar or lectins is of utmost importance since the system is directed to specific antigens or receptors on cell surfaces and consequently triggers receptor-mediated transcytosis for facilitated delivery of cargo molecule across the BBB. Receptors that are highly expressed on the endothelial cells of the BBB include but are not limited to: the insulin receptor, transferrin receptor, LDL receptor and its related protein, and others that are being currently explored [12]. For transporter-mediated delivery, that utilized by peptides and small molecule nutrients, the drug should mimic the carrier substrates to be transported, hence this approach necessitates careful consideration of the kinetics available to transport physiologic molecules, the structural binding requirements of the transporter and the appropriate drug modification that allows binding and transport without loss of activity in-vivo [13]. On the other hand, adsorptive-mediated endocytosis and transcytosis in contrast to receptor-mediated transcytosis, involve endocytosis in vesicles of charged substances without a specific mechanism [14]. Cationic peptides and proteins with a basic isoelectric point bind to the luminal plasma membrane via electrostatic interactions with anionic sites, subsequently adsorptive endocytosis is initiated. It was demonstrated that protein transduction domains (PTDs), TAT and polyarginines enhance brain uptake and bypass the P-gp efflux of some anticancer and peptide drugs.

Nanocarrier approach exploited in CNS drug delivery and targeting include micelles, liposomes and nanoparticles (nanospheres and nanocapsules) [8]. The aim is to enhance the specificity towards cells or tissues, to target the drugs and improve their permeation and uptake through biological membranes and/or to shield them from destructive enzyme action. By masking the physicochemical characteristics and encapsulation of drugs in these systems, nanocarriers could ferry non-transportable drugs across the BBB [15]. However, the fate of nanocarriers after intravenous administration and their biodistribution following "opsonisation" or their protection by conferring stealthness by pegylation should be considered in the design of efficient drug carrier systems. Despite its complexity, the design of nanocarriers with surface stealthness as well as specific ligand on their surface for active targeting to the brain offer an "Onion-like" model that has been claimed as a promising strategy for efficient brain delivery.

For recapitulation, the paramount concern about drug delivery to the brain has triggered research to focus on physiological and biopharmaceutical challenges that preclude drug access and identify chances in rational drug and delivery system design. The knowledge gained is revolutionizing the approach to drug-targeting and prodrug research. The integration of this research into early drug discovery to expand the chemical space of CNS-likeness drug molecules is highly appreciated. Meanwhile this calls for more interdisciplinary collaborations, and innovative use of new technologies to solve drug targeting problems in order to maximize the therapeutic outcomes for treatment of CNS diseases.

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