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Review article

The role of non-endothelial cells on the penetration of nanoparticles through the blood brain barrier

Rui Pedro Moura[a], Andreia Almeida[b,c,d], Bruno Sarmento[a,b,c,*]

[a] CESPU – Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, Rua Central de Gandra 1317, 4585-116 Gandra, Portugal
[b] INEB – Instituto Nacional de Engenharia Biomédica, Universidade do Porto, Rua Alfredo Allen 208, 4200-180 Porto, Portugal
[c] i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen 208, 4200-180 Porto, Portugal
[d] ICBAS – Instituto Ciências Biomédicas Abel Salazar, Universidade do Porto, Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal

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ABSTRACT

The blood brain barrier (BBB) is a well-established cell-based membrane that circumvents the central nervous system (CNS), protecting it from harmful substances. Due to its robustness and cell integrity, it is also an outstanding opponent when it comes to the delivery of several therapeutic agents to the brain, which requires the crossing through its highly-organized structure. This regulation and cell-cell communications occur mostly between astrocytes, pericytes and endothelial cells. Therefore, alternative ways to deliver drugs to the CNS, overcoming the BBB are required, to improve the efficacy of brain target drugs. Nanoparticles emerge here as a promising drug delivery strategy, due to their ability of high drug loading and the capability to exploit specific delivery pathways that most drugs are unable to when administered freely, increasing their bioavailability in the CNS. Thus, further attempts to assess the possible influence of non-endothelial may have on the BBB translocation of nanoparticles are here revised. Furthermore, the use of macrophages and/or monocytes as nanoparticle delivery cells are also approached. Lastly, the temporarily disruption of the overall organization and normal structure of the BBB to promote the penetration of nanoparticles aimed at the CNS is described, as a synergistic path.

Contents

Abbreviations: ALA, 5-aminolevulinic acid; AMT, Adsorptive-mediated transcytosis; BBB, Blood-brain barrier; B-CSF, Blood-cerebrospinal fluid barrier; CNS, Central nervous system; CSF, Cerebrospinal fluid; CYPs, Cytochromes P450; FUS, Focused ultrasound; GLUT-1, Glucose transporter 1; LDLR, Low-density lipoprotein receptor; PEG, Poly(ethyleneglycol); PEG-PLA, Polyethylene glycol-polylactic acid; PCI, Photochemical internalization; PTD, Photodynamic therapy; RM, Receptor-mediated transcytosis; TAT, Trans-activating transcriptor; TfR, Transferrin receptor.

* Corresponding author at: i3S, Instituto de Investigação e Inovação em Saúde, Rua Alfredo Allen, 208, 4200-18035 Porto, Portugal.
E-mail address: bruno.sarmento@ineb.up.pt (B. Sarmento).

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1. Introduction

The blood-brain barrier (BBB), referred for the first time by Paul Ehrlich in 1885, is an extremely limiting barrier that isolates the central nervous system (CNS) from the rest of the body (Rubin and Staddon, 1999). It is mainly composed of highly-specialized brain endothelial cells, which form complex and compact tight and adherents junctions, characterized also by the lack of fenestrations, high expression of efflux transporters and minimal pinocytic activity (Almutairi et al., 2016; Neuwelt et al., 2008; Tietz and Engelhardt, 2015). Joining these endothelial cells are the astrocytes and their respective end-feet, pericytes, macrophages, neurons and a basement membrane, constituted mainly by structural proteins. The basement membrane can be split up into two portions, the vascular basement membrane secreted mainly by endothelial cells and pericytes, and the glial basement membrane, secreted by astrocytes (Blanchette and Daneman, 2015). All the previously mentioned components, together with the endothelial cells, make up the neurovascular unit, a definition proposed to elucidate how the different interactions between these components ultimately regulates the BBB properties (Bradbury, 1985; Weiss et al., 2009).

Astrocytes have shown the ability to modulate several features of the BBB, such as promoting tighter tight junctions between the endothelial cells, regulating the number of receptors expressed on the surface of endothelial cells, managing the expression of certain transporters/efflux pumps, controlling the balance of fluid and electrolytes at the BBB, and also the ability to directly express efflux pumps to promote the removal of foreign compounds from the BBB (Abbott et al., 2006; Dombrowski et al., 2001; Rubin et al., 1991).

Pericytes have shown to be able to control the development of endothelial cells, and to have an high influence on the regulation of the rate of transcytosis occurring at the BBB and to regulate the vascular permeability and immune cell trafficking of the BBB (Dohgu et al., 2005). Taking this into account, the possible disruption of the interactions between the endothelial cells and astrocytes/pericytes may prove as a valuable tool in further increasing the permeability of molecules and other structures across the BBB as it may result in a periodical opening of this barrier (Berezowski et al., 2004).

Nanoparticles emerge as platforms to deliver drugs to the CNS due to their ability to cross the BBB without compromising its integrity and without exhibiting notable central or peripheral toxicity (Jain, 2012). Additionally, nanoparticles can increase the residence time of the drug in the body by circumventing certain physiological excretion mechanisms. Furthermore, nanoparticles load drugs and protect them from efflux pumps present in the endothelial cells, such as the P-glycoprotein, multidrug resistance proteins and breast cancer resistance proteins, overexpressed in the BBB endothelial cells (Gomes et al., 2014; Grabrucker et al., 2014).

Nanoparticles may be prepared by a wide variety of materials, from polymers, lipids to inorganic materials. Based on their constitution and possible coating agents that can be added to ensure interaction with specific transport pathway, nanoparticles will cross the BBB mainly through receptor mediated transcytosis and adsorptive-mediated transcytosis (Saraiva et al., 2016). Therefore, the mechanisms of nanoparticle BBB-crossing may be intimately associated with the regulation of both astrocytes and pericytes exert on the BBB; either through chemical segregations or by direct cell-cell signalling, increasing or decreasing the amount of receptors and/or transporters expressed or the rates of transcytosis occurring in the endothelial cells (Abbott, 2013; Prat et al., 2001). Furthermore, nanoparticles can also be develop to target non-endothelial cells in certain situations to achieve BBB penetration and a therapeutical action in certain CNS disorders (Gu et al., 2017). Macrophages and monocytes have also been explored as drug delivery candidates to the CNS, due to their ability to incorporate nanoparticles, and to cross the BBB as local immune cell (Klyachko et al., 2014).

This review aims to summarize the role that non-endothelial cells of the BBB hold, and their possible interaction and regulation of the penetration of nanoparticles through the BBB. Moreover, methods that use a temporary disruption of the BBB, either physically or through chemical segregations affecting astrocytes and/or pericytes will also be presented.

2. General overview of the blood-brain barrier structure

The BBB is the main physiological barrier that isolates the CNS, holding the ability to perform physiological actions to ensure the homeostasis of CNS. The main roles of the BBB are to regulate the passage of substances to the brain, to maintain a correct environment for all neuronal activities, to block the passage of potentially toxic compounds and pathogens and to allow a correct and fluid communication between the brain and the rest of the body (Campos-Bedolla et al., 2014). To complete its functions, a very delicate balance is maintained by the endothelial cells which, with assistance of all the components of the neurovascular unit, act as a team to correctly safeguard the CNS (Abbott et al., 2006; Balabanov and Dore-Duffy, 1998).

The biggest feature that allows the well-known selective behaviour in the BBB is mainly the existence of highly specialized tight junctions between endothelial cells, that are responsible for the intrinsic high BBB trans-endothelial electrical resistance, and contrary to the lower values reported to other vascular endothelial cells (Stamatovic et al., 2008). Considering all the limiting factors of the BBB presented, only very specific substances and/or endogenous compounds, or highly lipophilic, small-sized drugs can cross the BBB through specific pathways. Those include a paracellular pathway, directly through the tight junctions between the endothelial cells (mainly for small and water soluble agents); a direct pathway in which compounds can directly cross the cell, through diffusion (applicable only by very small and lipophilic molecules, or certain gaseous molecules such as O_2 and CO_2; through transport proteins that exist on endothelial cells to transport certain nutrients/compounds required in the CNS; cell surface receptor mediated transcytosis, in which a compound interacts with a receptor expressed on the surface of the endothelial cell, and is interiorized; non-cell surface-receptor mediated transcytosis, or adsorptive transcytosis, in which a compound does not require a receptor or a transporter to be internalized by the endothelial cell (Pinto et al., 2017). Out of the pathways presented, certain drugs exploit them to adequately cross the BBB. Some of these pathways are also effectively used by nanoparticles to cross the BBB with relative efficiency and limited side effects (Li et al., 2017). After crossing the BBB, drugs face a second barrier, the blood-cerebrospinal fluid barrier (B-CSF). Unlike its other barrier counterpart, the B-CSF is relatively permeable to most drugs. After crossing to the cerebrospinal fluid (CSF), drugs will cross into the brain parenchyma, through diffusion. However, the diffusion process is founded to be very slow, usually resulting in much higher concentrations of free drug in the CSF than in the brain parenchyma. Therefore, due to the accumulation at the CSF, toxicity can occur (Pardridge, 2011). Nanoparticles hold an additional advantage, due to the ability to hold within numerous molecules. Also, the CSF can promote drug movement to the brain parenchyma through Virchow-Robin (perivascular) spaces. However, as this pathway has low rates of fluid flow, it is usually not considered important for drug transport to the brain parenchyma (Pardridge, 2011; Rennels et al., 1985). Nanoparticles can also enter the brain parenchyma through the