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Review Article

Blood–brain barrier models and their relevance for a successful development of CNS drug delivery systems: A review

Joana Bicker [a,b], Gilberto Alves [b,c,*], Ana Fortuna [a,b], Amílcar Falcão [a,b]

[a] Laboratory of Pharmacology, University of Coimbra, Coimbra, Portugal
[b] CNC – Centre for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal
[c] CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal

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8-((4-chlorophenyl)thio)cyclic-3',5'-AMP
Dodecane
Fluorescein isothiocyanate
Hydrocortisone
Inulin
Propranolol
Sodium fluorescein
Sucrose
Vinblastine

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ABSTRACT

During the research and development of new drugs directed at the central nervous system, there is a considerable attrition rate caused by their hampered access to the brain by the blood–brain barrier. Throughout the years, several *in vitro* models have been developed in an attempt to mimic critical functionalities of the blood–brain barrier and reliably predict the permeability of drug candidates. However, the current challenge lies in developing a model that retains fundamental blood–brain barrier characteristics and simultaneously remains compatible with the high throughput demands of pharmaceutical industries. This review firstly describes the roles of all elements of the neurovascular unit and their influence on drug brain penetration. *In vitro* models, including non-cell based and cell-based models, and *in vivo* models are herein presented, with a particular emphasis on their methodological aspects. Lastly, their contribution to the improvement of brain drug delivery strategies and drug transport across the blood–brain barrier is also discussed.

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Abbreviations: ABC, adenosine triphosphate-binding cassette; AJ, adherens junction; AMT, adsorptive-mediated transcytosis; AP, alkaline phosphatase; AQP-4, aquaporin-4; BBB, blood–brain barrier; Caco-2, human epithelial colorectal adenocarcinoma cell line; cAMP, adenosine 3′,5′-cyclic monophosphate; CEC, cerebral endothelial cell; CNS, central nervous system; CPT-cAMP, 8-(4-chlorophenylthio)-cAMP; CSF, cerebrospinal fluid; CYP, cytochrome P450; FITC, fluorescein isothiocyanate; HUVEC, human umbilical vein endothelial cell; K_p, ratio of brain and plasma concentrations at steady-state; $K_{p,uu}$, ratio of unbound concentrations in the brain interstitial fluid and plasma at steady-state; log BB, logarithm of the ratios of brain and plasma concentrations or areas under the curve; MDCK, Madin–Darby canine kidney cells; OAPs, orthogonal arrays of particles; PAMPA, parallel artificial membrane permeability assay; PBL, porcine brain lipids; P_e, effective permeability; P-gp, P-glycoprotein; PML, plon membrane lipid; PS, permeability surface area product; RMT, receptor-mediated transcytosis; SLC, solute-carrier transporters; TEER, transendothelial electrical resistance; TJ, tight junction; UWL, unstirred water layer; VB-Caco-2, vinblastine-treated Caco-2; ZO, zonula-occludens.

* Corresponding author. Faculty of Health Sciences, University of Beira Interior, CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal. Tel.: +351 275329002; fax: +351 275329099.
E-mail address: gilberto@fcsaude.ubi.pt (G. Alves).

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1. Introduction

During the discovery and development of novel drugs directed at the central nervous system (CNS) the attrition rate is even higher than in other therapeutic areas [1], because the complexity of the blood–brain barrier (BBB) hampers the entry of the chemical entities into the brain, causing an insufficient CNS exposure for the compound to be pharmacologically effective. The truth is that approximately 100% of large-molecule neurotherapeutics and over 98% of small-molecule compounds never reach the market due to an inherent inability to cross the BBB [2]. Hence, the BBB is frequently regarded as the bottleneck of the successful development of CNS-acting drugs [2]. In contrast, for peripherally-active drugs, BBB permeation should be avoided as undesirable side effects may occur [3]. For this reason, several *in silico*, *in vitro* and *in vivo* models have been developed and optimized for screening compounds according to their permeability across the BBB [4–7]. Particularly, *in vitro* and *in vivo* models of the BBB have contributed to the diversity of CNS drug delivery systems that lately emerged, by allowing an estimation of their biodistribution and brain uptake [8].

Over the years, *in vivo* methodologies based on the measurement of total brain concentrations and brain/plasma ratios of drug candidates on rodents have been applied in CNS drug discovery programs. In fact, *in vivo* brain uptake experiments provide the most reliable information for assessing the brain penetration ability of test compounds. However, due to the large number of molecules generated by combinatorial chemistry, they cannot be applied as high throughput screening assays in early drug discovery stages. Thus, although most pharmaceutical companies use them as part of the routine biopharmaceutical profiling of compounds [9], *in silico* and *in vitro* methodologies are essential to distinguish the candidates that must be eliminated or structurally modified from the promising candidates that can move forward in the development process [9,10]. Nonetheless, the validation of these methodologies is indispensable and involves the use of *in vivo* results as Ref. [11].

The purpose of this review is to discuss the features of the most currently relevant *in vitro* and *in vivo* BBB models, as well as their role in the evaluation of the permeability of CNS drug candidates and drug delivery systems in the early phases of drug discovery and development programs. The unique structural and functional characteristics of the BBB are firstly referred, followed by an overview of the main *in vitro* and *in vivo* models of the BBB. The last section of this review illustrates the impact of these models in the effective development of CNS drug delivery systems. Despite their recent application in CNS drug discovery, *in silico* models will not be focused in the scope of this review.

2. The BBB and the neurovascular unit

The molecular exchanges between the blood and the neural tissue or its fluid spaces are limited and essentially regulated by three barriers: the blood-cerebrospinal fluid (CSF) barrier, formed by the epithelial cells of the choroid plexus facing the CSF; the avascular arachnoid barrier that completely encloses the CNS under the dura mater; and the BBB [11]. Although these three interfaces form barrier layers between the CNS and the blood, the BBB, composed by cerebral endothelial cells (CECs) that delimit cerebral microvessels, is considered the major site of blood–CNS exchange and responsible for maintaining the homeostasis of the CNS [12,13]. The CECs, together with astrocytes, pericytes, microglia, neurons and the extracellular matrix, form the neurovascular unit (Fig. 1), a highly coordinated system that dynamically regulates the cerebral microvascular permeability and provides a basis for understanding the development and physiology of the BBB, including the mechanisms by which cerebral microvascular permeability can be influenced by drugs and diseases [14–17].

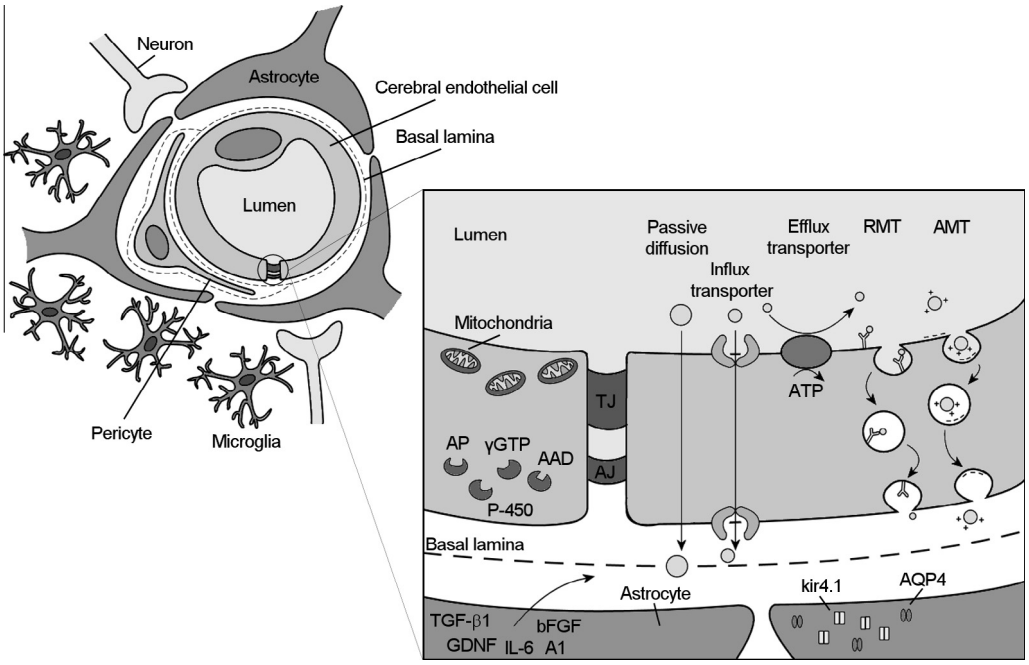

Fig. 1. Structural representation of the blood–brain barrier (BBB) and routes of transport. The BBB is a complex system composed by cerebral endothelial cells, separated from pericytes and astrocytic end-feet by the basal lamina. Microglia and neurons are also part of the neurovascular unit. The routes of transport across the BBB are shown in greater detail, as well as, several endothelial enzymes and regulatory factors released by astrocytes. The molecular organization of tight junctions (TJs) and adherens junctions (AJs) is not depicted. A1, angiopoietin 1; AAD, aromatic acid decarboxylase; AMT, adsorptive-mediated transcytosis; AP, alkaline phosphatase; AQP-4, aquaporin-4; ATP, adenosine triphosphate; bFGF, basic fibroblast growth factor; CYP, cytochrome P450; GDNF, glial-derived neurotrophic factor; γ-GTP, γ-glutamyl transpeptidase; IL-6, interleukin-6; Kir4.1, potassium channel; RMT, receptor-mediated transcytosis; TGF-β1, transforming growth factor-β1. *Adapted from* Refs. [12,15].

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