



Modelling of the Blood-Brain Barrier-Keeping Hold of the Old, with a View to the New



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Introduction

Disorders of the central nervous system (CNS) have significant impact at both the individual and societal level. The steady increase in the mean age of the population, and the subsequent increase in incidence of age-related CNS disorders, has ultimately increased the value of the multi-billion-dollar industry of neurotherapeutics. Neurological healthcare in Europe alone is trending towards annual costings of \$1 trillion dollars [1], with an estimated increase of 85% by 2030 [2]. These pressures make the development of effective treatments a high priority.

The main obstacle in the development of these therapies is the blood-brain barrier (BBB); a near-impenetrable, dynamic structure that regulates the bi-directional exchange of endogenous/exogenous macromolecules, solutes, and fluids between the brain parenchyma and circulating blood of the cerebral microvasculature. The plethora of processes acting in unison, to maintain BBB integrity and preserving homeostasis of the neural cavity, are of huge clinical importance-in different pathological settings dysregulation of particular characteristics that protect and regulate the brain environment from foreign insult have been linked to the onset and development of neurological disorders, whilst remaining defences in each respective setting concurrently makes effective drug delivery to the brain and treatment of the disorder an incredibly difficult task [3].

Consequently, quantitative in vitro BBB penetration studies are becoming an increasingly integral part of drug discovery programs-an indication of the importance of such in the design and delivery strategies of prospective CNS directed therapies [4]. Oft preceding both animal and clinical studies, these preliminary precautionary measures have however significantly increased the drug-development timeline [5]. The development and introduction of better translational in vitro research models is therefore regarded as a priority to not only reduce the average time-line, but also reduce the prospective risks that are often encountered in the preclinical development of CNS therapies.

As alluded to, the BBB presents a very sophisticated and unique behaviour and architecture, making its recapitulation one of the

greatest current challenges in the therapeutic design field. The development of models has subsequently revolved around three fundamental aspects:

- (i) Suitable BBB cell types
- (ii) Three-dimensional multicellular modelling of the neurovascular unit and
- (iii) Integration of hemodynamic forces.

In its most basic form, and the most commonly used BBB model, particularly for permeability-orientated studies, is the cell type that embodies the BBB at its most fundamental level-the brain microvascular endothelium [6]. Early BBB models utilised epithelial cell lines of non-cerebral origin such as MDCKs and Caco-2 [7]. These pseudo-BBB models initially, and presently, offer a robust means of assessing monolayer permeability owing to their highly upregulated intercellular junctions (like that of the brain endothelium). Over the last five decades, BBB research has benefitted from methodological advancements that enabled the successful isolation, implementation and investigation of cerebral microvascular endothelial cells [8,9], significantly advancing our understanding of BBB behaviour. Despite these advancements the original epithelial cell-based pseudo-models continue to be used today; frequently considered more appropriate models of the BBB over even human primary-isolated endothelia, albeit for a limited number of biological aspects.

For it is important to consider how these cultures behave once removed from their physiological environment. Many primary and immortalised cell monocultures have demonstrated morphological and functional changes ex-vivo ultimately leading to the transient diminishment of important BBB characteristics; an aspect that has hindered models on both ends of the scale for complexity [10]. Consider the supporting cell types that, along with the endothelial cells, are recognised as promoting the BBB phenotype and collectively form the neurovascular unit (NVU); namely pericytes, astrocytes, neurons and microglia. Recent studies have identified their contact with the endothelium, from both a physical contact

and secretome perspective, to be of considerable importance to overall BBB phenotype [11], and as a consequence effort have been made to incorporate their collective input into BBB modelling. Whilst “in-direct” contact, “non-contact”, and “pseudo-contact” co-culture approaches, with up to four different cell types, have been shown to significantly influence BBB endothelial behaviour, similar cell-specific limitations that were previously mentioned with respect to endothelia also pertain to these extra-capillary supporting cell types [12].

Taken together, efforts taken within the field of multi-cellular BBB modelling have shown the target-structure vastly complex to mimic in vitro and thoughts on the correct approach has spawned considerable debate within the field. Moreover, the situation of complete recapitulation of the BBB is further complicated owing to the importance of the often overlooked, but increasingly appreciated, influence of the hemodynamic environment on BBB endothelia phenotype. Indeed, the associated forces exerted on the endothelial monolayer by fluid flow have been shown to be a critical influencer of cell phenotype [13,14], and the impetus to incorporate these environmental cues into what is already a complex multicellular model with various approaches already reported [15,16].

In summary; while there is arguably an unmet need for a more physiologically relevant and predictive human BBB model, the materials, apparatus, and approaches for in vitro BBB modelling have advanced significantly over the last 50 years and have contributed significantly to BBB research. While dynamic multicellular flow-mediated systems are now readily available, widely used, and increasing in number and use, static monocultures still have significant application and value within the appropriate research setting. It is therefore of utmost importance that researchers embrace both old and new approaches to BBB modelling (including in silico modelling) such that the most accurate representation of the biological aspect of interest is embodied. Only in this way will the process of developing pharmacologically promising drug candidates be significantly advanced leading to improved timelines for therapeutic development against CNS-specific pathologies.

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