Toward a Humanised Alternative to the Use of Laboratory Animals for Blood-Brain Barrier Research

Adjanie Patabendige

Central nervous system (CNS) diseases have a devastating impact on the quality of life of those affected, with large health economic and social costs globally. There are no effective treatments for many neurological diseases, including almost all viral brain infections. A major hurdle in treating CNS disease is transporting therapeutics across the blood-brain barrier (BBB). The BBB is formed by the endothelial cells that line cerebral capillaries, supported by cells of the neurovascular unit (NVU) that induce and maintain the properties of the BBB. The main function of the BBB is to restrict the entry of molecules and pathogens into the CNS and maintain brain homeostasis, which is essential for normal neuronal function. The BBB is a major challenge in drug discovery programmes, as many potential CNS drugs cannot cross the BBB due to its strict regulation of paracellular and transcellular entry of molecules. To develop better treatment strategies, we need to increase our understanding of BBB function during health and disease. Evidence of the role of the BBB during viral pathogenesis has traditionally come from studies on animals, because of the difficulties associated with conducting clinical studies in humans and obtaining human brain tissue for in vitro investigations. There are several good in vitro BBB models derived from animal tissue, but as I have outlined in a Comment to be published in ATLA, there is an urgent need for the development of realistic human BBB models that can mimic the in vivo characteristics of the BBB.1

BBB research is a comparatively new field, as the existence of a BBB was only discovered just over 100 years ago. Publications on the BBB have steadily increased — from just one paper in 1947 to over 1500 papers so far this year — as we begin to understand the importance of the BBB in neurological disease (Figure 1). My interest in BBB research, and particularly in the development of in vitro BBB models, stemmed from discovering at the very beginning of my research career that only a handful of good in vitro BBB models were available. A major limitation was that most of these models were not robust and simple enough to use in the pharmaceutical industry for drug permeability studies. Furthermore, many pharmaceutical companies used in vitro BBB models derived from epithelial tissue (e.g. MDCK cells, Caco-2 cells), rather than from brain endothelial origin for their early-phase CNS drug discovery studies.

To address these issues, I established a simple to use and robust in vitro BBB model, derived from porcine brain endothelial cells that expressed major BBB features. Porcine brain material was used, because it was a by-product of the meat industry, so the availability of this type of brain tissue was not an issue. Furthermore, the anatomy, physiology and genome of the pig, all reflect those of the human more closely than most laboratory animal models. Therefore, a porcine BBB model seemed to be the best alternative to a human model for drug discovery studies.

Having established a porcine BBB model, I moved onto developing an in vitro human model, because of my interest in studying the role of the BBB during CNS infection. Mechanisms of pathogen entry to the brain are poorly understood for many brain infections (e.g. viral encephalitis, bacterial meningitis, parasitic brain infections). I used this static human model to investigate how viruses that cause encephalitis cross the BBB. The static human model has given some interesting insights into the complex interactions between the virus and the BBB, and the role of inflammatory cytokines in viral pathogenesis (manuscript in preparation). However, replicating all the main features of the human BBB in vitro is not an easy task. The main challenges are the availability of fresh human brain tissue and maintaining BBB morphology and function in culture, following isolation of the cells. Immortalised human brain endothelial cells are an alternative, but these may lack certain important BBB features because of the immortalisation process. To overcome these challenges, I am now attempting to establish a flow-based three-dimensional (3-D) BBB model for studying the role of the BBB in brain infections (funded by an NC3Rs David Sainsbury fellowship). A flow-based model is preferred to a static model, as the shear stress caused by blood flow is important in maintaining the BBB features of brain endothelial cells, and will also provide the right environment for leukocyte transmigration across the endothelium, which is an important physiological process during infection. A realistic human BBB model will help increase our understanding of the importance of the BBB in protecting the brain during infection, as well as the damage caused to the BBB during the course of the infection. Furthermore, this flow-based 3-D human BBB model will potentially lead to the generation of physiologically-relevant human data and the identification of targets for developing novel therapeutics. If successful, it will be a useful alternative to laboratory animals for studying the BBB in CNS disease.
Figure 1: Blood-brain barrier research papers published, by year

A PubMed search was performed on 19.10.12. Search term = blood–brain barrier; Field = Title/Abstract.

References


