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feature

Models for predicting blood–brain barrier permeation

Peter Aadal Nielsen[1], Olga Andersson[1], Steen Honoré Hansen[2], Klaus Bæk Simonsen[3] and Gunnar Andersson[1,*], ga@entomopharm.dk

The endothelial blood–brain barrier (BBB) ensures an optimal environment for proper neural function in vertebrates; however, it also creates a major obstacle for the medical treatment of brain diseases. Despite significant progress in the development of various *in vitro* and *in silico* models for predicting BBB permeation, many challenges remain and, so far, no model is able to meet the early drug discovery demands of the industry for reliability and time and cost efficiency. Recently, it was found that the grasshopper (*Locusta migratoria*) brain barrier has similar functionality as the vertebrate BBB. The insect model can thus be used as a surrogate for the vertebrate BBB as it meets the demands required during the drug discovery phase.

Introduction

The complex neural function of the central nervous system (CNS) depends on a highly stable environment, enabling proper firing and communication of its neurons. In vertebrates, such environment is obtained by a sophisticated blood–brain barrier (BBB), consisting of a single layer of microvascular endothelial cells that prevent the free movement of molecules from the blood into the brain, thus contributing to the homeostasis of the microenvironment. Paracellular diffusion of hydrophilic compounds is prevented by the BBB endothelial cells as a result of lateral transmembrane proteins, which form the so-called 'tight junctions'. In addition, ATP binding cassette transporters are asymmetrically located at the humoral side of the endothelial cells, preventing the entry of the majority of invading xenobiotics by efflux mechanisms [1,2].

The preservation of a proper microenvironment in the vertebrate brain, including that of humans, by a BBB also therefore prevents therapeutic drugs from entering the brain. Consequently, the BBB is a major obstacle in the discovery of new drugs for efficient treatment of CNS-related diseases. For this reason, effective CNS drug discovery programs require early information about the ability of compounds to permeate the BBB and reach their intended brain targets. By contrast, programs targeting peripheral organs also need to investigate the BBB permeability of the compounds to avoid CNS side effects. Therefore, it is of the utmost importance to address the BBB permeability during the early drug discovery phases and this requires BBB models that are useful in guiding the drug discovery process, including drug design.

Status of BBB permeation models

Techniques used for the prediction of the BBB permeability of chemical compounds have been repeatedly scrutinized for their reliability and utility [3–6]. In 2004, Abbott reviewed the status of the most commonly used technologies for measuring or predicting the BBB permeation of drug discovery compounds in vertebrates [7]. In agreement with Abbott, we conclude that *in vivo* and *in situ* rodent models for studying BBB permeation are not time and cost efficient enough to be applied as screening models during the early drug discovery phases; we have therefore omitted these models from the following discussion.

Furthermore, Abbott pointed out that there is no simple *in vitro* model that sufficiently covers the brain uptake functionalities. There is, therefore, also a need for new, more reliable, yet simple models to test BBB permeation. No single model (cell-based or non-cell-based) is thus available that can meet the requirements of the drug discovery phase. Consequently, companies have to consider using results from various *in vitro* models and techniques that, when combined, fulfill the criteria required to substitute *in*

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