7 Drug Transport Across the Blood–Brain Barrier

G. Fricker

7.1 Introduction ........................................... 139
7.2 Anatomy of Brain Capillaries .......................... 141
7.3 Transport Processes at the Cerebral Endothelium .... 142
7.4 In Vitro Models for Studying the Function Blood–Brain Barrier . 146
7.5 Conclusion and Perspectives ............................. 150
References ...................................................... 151

7.1 Introduction

Case numbers of neurodegenerative disorders, such as Alzheimer’s disease, Morbus Parkinson, epilepsy, brain tumours or human immunodeficiency virus (HIV)-related encephalopathy, are continuously increasing, thereby causing enormous costs to the public economy. For example, following the World Health Report, more than 12 million people are suffering from Alzheimer’s disease worldwide. With more than 4 million patients at an annual expense of over US $50 billion, the disease has currently become the third largest medical problem in the United States (Friden 1996).

Unfortunately, many drug candidates for treatment of these disorders have high efficacy in pharmacological in vitro models, but are of little or even no effect in patients. One major problem in the CNS disease management is the restricted access of exogenous compounds to the brain. They have to pass across the endothelial cells of brain capillaries,
in vitro
• isolated microvessels
• cultured capillary endothelial cells
• co-cultures with astrocytes or pericytes

in situ
• brain uptake index
• brain efflux index
• microdialysis

in vivo
• effect models

advantages
• defined conditions
• long term viability

• intact organ
• 3-dimensional structure

• intact organ
• 3-dimensional structure

disadvantages
• lack of cellular environment
• monolayer tightness
• cells dedifferentiating

• organ damages
• leakage

• "black box"
• mechanistic information (?)

Fig. 1. Summary of experimental models to study drug transport across the blood–brain barrier

which form the so-called blood–brain barrier. This barrier maintains the physiological homeostasis required for a proper cerebral function (Paulson et al. 1999). Investigation of the functional properties of the blood–brain barrier is difficult because it is not directly accessible in vivo. Therefore, efforts are ongoing to develop representative cellular in vitro models that mimic its structural and functional characteristics (Greenwood et al. 1995) and may help to understand the regulation of the barrier function. Figure 1 summarises available models of different complexity with their advantages and disadvantages on various biological levels ranging from relatively simple cells culture systems up to brain perfusion techniques. Purpose of this article is to give a short overview on these models and the possibilities they offer for studying