Therapeutic considerations in BBB transport changes during CNS diseases

De Lange ECM
Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Leiden University, Leiden

Drug transport across the blood-brain barrier (BBB) is determined by the BBB functionality, cerebral blood flow, plasma protein binding, and the physicochemical properties of the (free) drug. Apart from diffusion, active BBB transport may occur by membrane transporters such as the P-glycoprotein and the multidrug resistance-associated proteins (MRPs). For many drugs, BBB transport has important implications for the relation between drug treatment and
central drug effects. It is hypothetised that changes in BBB transport initiate and/or contribute to CNS diseases, while on the other hand the therapeutic action of (chronic) drug treatment of CNS disorders are strongly influenced during induced changes in the functionality of the BBB.
Our research is focussed on the relation between neurodegenerative processes in the brain and the BBB transport characteristics as a function of disease progression, in a time-dependent and quantitative manner. Intracerebral microdialysis is used in these investigations to measure the free brain extracellular fluid concentrations of drugs as well as to search for potential in vivo biomarkers of neurodegeneration, and is combined with serial blood sampling. These data will be compared with ex-vivo analysis of brain tissue of classical histological markers
of neurodegenerative processes. Current experiments use the cortical stimulation rat model of epilepsy and the rotenone rat model of Parkinson's disease.
Here we present the results on the cortical stimulation model. BBB transport of the antiepileptic drug gabapentin is measured following electrical stimulation to a generalized
seizure (GS), and is compared with data following sham stimulation. The first series of experiments indicate an increase in transport of gabapentin into the brain following a single GS relative to sham conditions. These data are used for the optimal design of a new series of experiments with repetitive GS induction, within different time-frames.

Elizabeth CM de Lange, Leiden/Amsterdam Center of Drug Research, Division of Pharmacology, PO Box 9503, 2300 RA, Leiden, 071-5276330, l.lange@lacdr.leidenuniv.nl

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