The role of MDR1 P-glycoprotein and multidrug resistance-associated protein in medically intractable temporal lobe epilepsy

Summary / Zusammenfassung
Temporal lobe epilepsy (TLE) associated with hippocampal sclerosis and other forms of focal epilepsies comprise the most frequent medically intractable epilepsies. Among the various reasons for the pharmacoresistance of these disorders, it has been suggested that inadequate intraparenchymal drug concentration represents a possible mechanism of resistance to antiepileptic drugs. MDR1 P-glycoprotein (Pgp) and the multidrug resistance-associated proteins (MRP) are two energy-dependent efflux pumps which have been localized in brain endothelial cells and in choroid plexus. To assess whether there is a link between Pgp and drug-resistant epilepsy we analyzed the expression and function of these transporters on cryosections and on primary cultures of human microvascular endothelial cells (MVEC) from epileptic patients with hippocampal sclerosis as compared with MVEC isolated from normal brain cortex. In addition, the mRNA levels for MDRs and MRPs were investigated by quantitative RT-PCR analysis. The analysis revealed that all three transporters, Pgp, MRP1, and MRP2, were expressed in the small hippocampal areas resected by selective amygdalohippocampectomy. Pgp and MRP1 were expressed not only on endothelium but also by parenchymal cells. MRP2 was found on endothelium in the hippocampus. In contrast to MVEC from epileptic patients, control MVEC did not show any MRP1 and MRP2 expression. Pgp activity was seen in both MVEC from control and epileptic patients whereas MRP was only found in MVEC from epileptic patients.

To identify additional genes which might be involved in medically intractable epilepsy we performed microarray analysis on resected tissue from TLE patients. Surprisingly we found a strong and unexpected upregulation of autoimmune and inflammatory response genes in both hippocampal parenchyma and endothelial cells. These include interleukins (IL-1) chemokines (CCL3, CCL4, CXCL8) and their receptors (CXCR4). These results stand in striking contrast with the general belief that hippocampal sclerosis in TLE is not accompanied by an inflammation. We are therefore performing a detailed analysis of mRNA and protein expression of these genes and other genes of interest found to be up- or down-regulated in this study. The analysis will be performed in resected hippocampal tissue and MVEC of TLE patients as well as in the kainate mouse model of TLE.

Publications / Publikationen

Keywords / Suchbegriffe
blood-brain barrier, drug resistance, epilepsy, hippocampal sclerosis, multidrug resistance-
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