In vivo verification of efflux transporter interactions at the blood-brain barrier in rodents.

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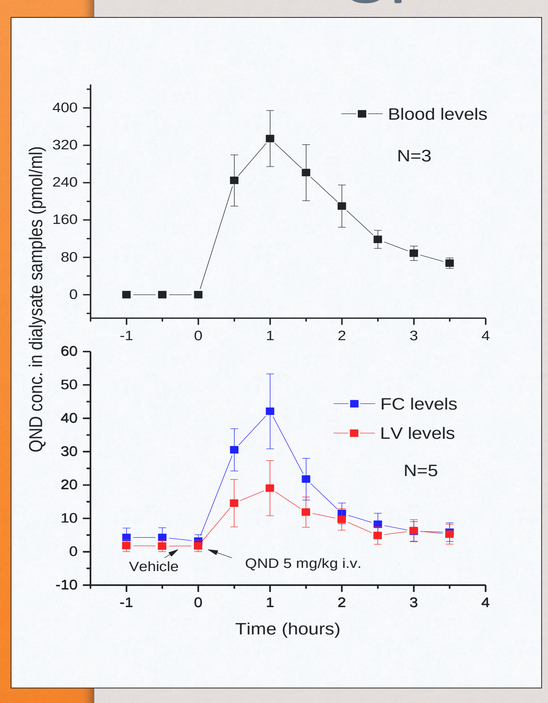
Introduction: The toxic events caused by membrane transporter - associated drug-drug interactions came in the focus of pharmacokinetic/pharmacodynamic studies during the last decade. One of the most important targets for drug therapy is the central nervous system itself. However, delivery of the drug accross the blood-brain barrier to the brain is often challenging. Apically localized efflux transporters are thought to be responsible for limited brain exposure of substrate drugs. Inhibition of these transporters by co-treatment with a transporter inhibitor may help to reach the appropriate central efficiency of the drug. The aim of our study was to investigate drug-drug interactions at the two major efflux transporter proteins (P-gp and BCRP) at the blood-brain barrier.

Methods: The P-pg interactions were studied using quinidine and PSC-833 as a reference substrate/inhibitor combination utilizing a triple probe microdialysis technique in rats. One probe was implanted in the frontal cortex, the second one in the lateral ventricle and the third one in the jugular vein. The BCRP interactions were studied by teriflunomide and Ko-143 substrate/inhibitor combination using dual-probe microdialysis in mice. The central probe was placed into the frontal cortex and the peripheral probe into the jugular vein.

Results

P-gp interactions



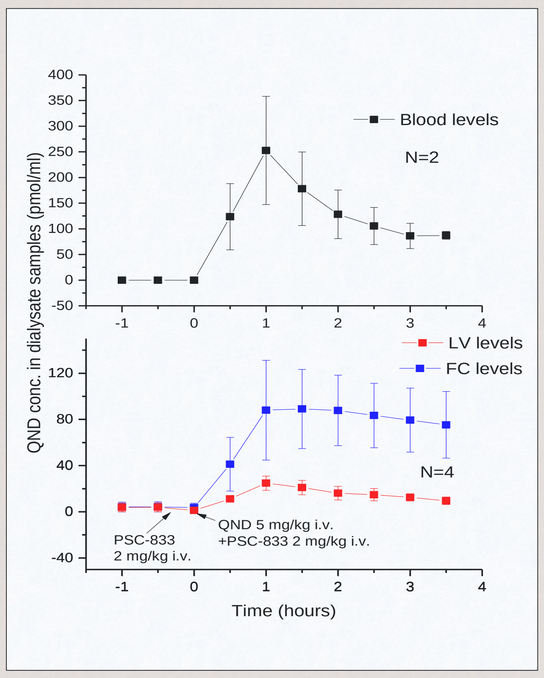


Figure 1. Concentration-time profiles of quinidine (5 mg/kg) after IV administration in rats. The concentration changes are monitored in blood, brain frontal cortex (FC) and lateral ventricle (LV) in control group (left panel) and in inhibitor treated (PSC-833 2x2 mg/kg) (right panel) animals.

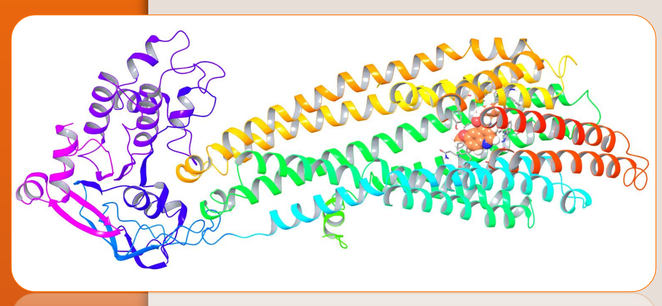


Figure 4. Docking of P-gp-Quinidine binding

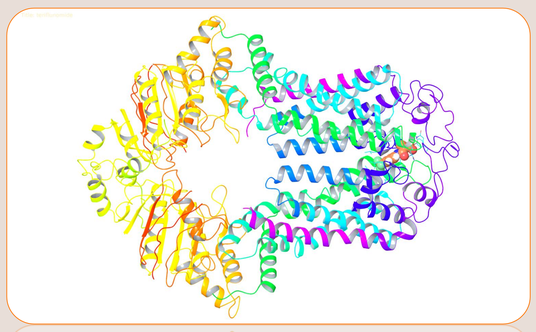
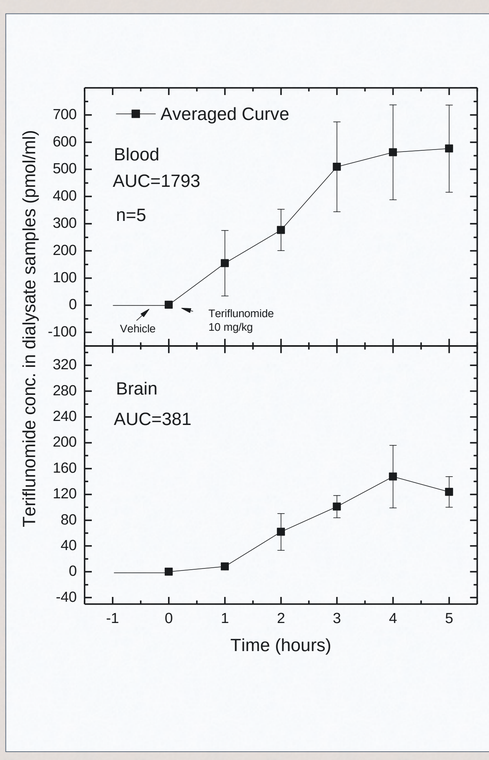


Figure 5. Docking of BCRP-Teriflunomide binding

BCRP interactions



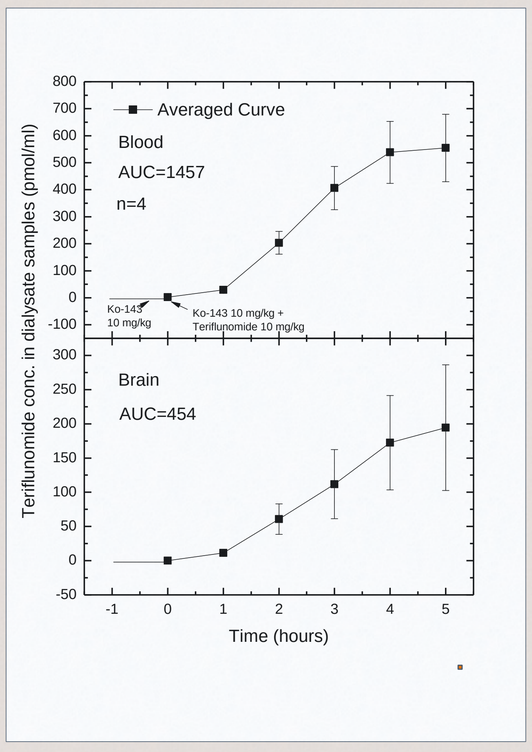
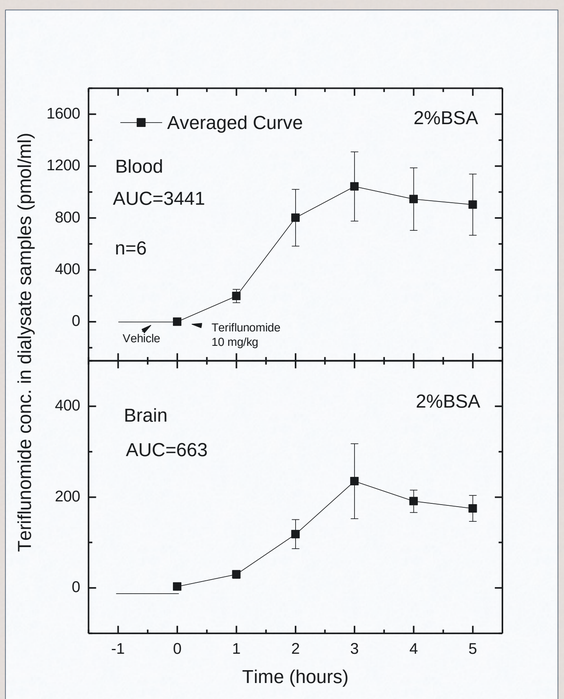


Figure 2. Concentration-time profiles of teriflunomide (10 mg/kg) after i.p. administration in the blood and brain in mice. Controls (left panel) received vehicle 20 min prior to teriflunomide treatment. The inhibitor treated group (right panel) received Ko-143 (10 mg/kg i.p.) prior to and also as a co-treatment with teriflunomide. The flow rate was 0.5 μL/min.



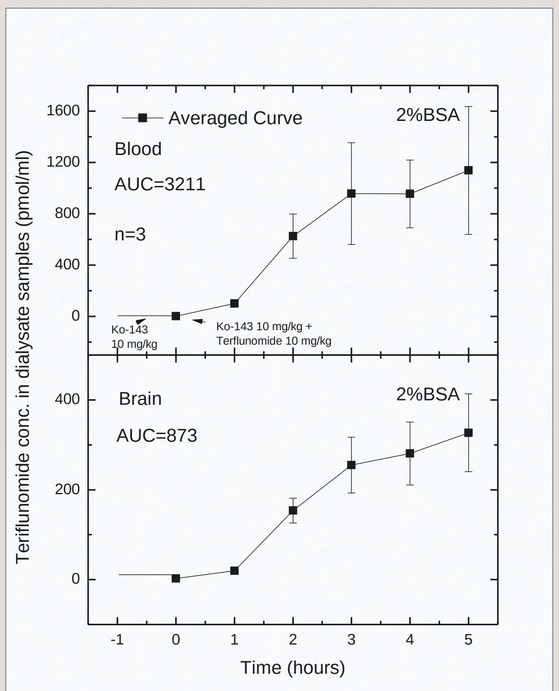


Figure 3. Concentration-time profiles of teriflunomide (10 mg/kg) after i.p. administration in the blood and brain in mice. Controls (left panel) received vehicle 20 min prior to teriflunomide treatment. The inhibitor treated group (right panel) received Ko-143 (10 mg/kg i.p.) prior to and also as a co-treatment with teriflunomide. Peripheral probes were perfused with 2% BSA containing peripheral perfusion fluid, the brain probes were perfused with 2%BSA containing artificial cerebrospinal fluid at a flow rate of 0.5 μL/min.

Discussion: Our microdialysis assay seems to be a proper technique for testing P-gp/BCRP and substrate drug interactions in vivo. The brain exposure to quinidine in rats and teriflunomide in mice remarkably increased after pretreatment with the transporter inhibitor. The characteristic of P-gp interaction with quinidine at the BBB and BCSFB were different most probably due to different orientation of the transporter at the two barriers (Fig.1). The sensitivity of the assay and the probe recovery were impoved after adding BSA to the perfusion fluid in teriflunomide experiments (Fig2-3).

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References:

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