Transporter Regulation at the Blood-Brain Barrier and in the Kidney

The blood-brain barrier is a unique dynamic regulatory interface that separates the blood stream from the interstitiel fluid of the brain parenchyma. Localised at the brain microvessel endothelium, the blood-brain barrier together with pericytes, astrocytes and microglia provides a precise homeostatic neuronal environment and means a key determinant in drug transport to the brain. Solute carriers like glucose (Slc2a1), amino acid (and organic cation transporters (Slc22a1-3), efflux transporters (P-glycoprotein (Abcb1)), Breast cancer resistance protein (Abcg2), Multidrug resistance-associated proteins 2/ 4 (Abcc2/ 4), tight junctions (Occludin, Claudin-5, ZO-1) as well as receptor-mediated endocytotic processes (RAGE, LRP1) selectively deliver essential nutrients and peptides to the brain or remove neurotoxic agents into the blood and thus, protect the brain from infections and injury. These blood-brain barrier elements respond to a variety of regulatory signals making them susceptible to profound changes that occur during CNS diseases or pharmacotherapy.

Similarly, these transporters are also highly expressed in other specialized barrier tissues, like renal proximal epithelial tubules, where they, along with xenobiotic metabolizing enzymes (CYP450 family), provide the excretion of potentially toxic compounds and metabolites into the urine. Renal drug excretion comprises glomerular filtration, tubular secretion and tubular reabsorption mechanisms; the two latter are mediated via uni- and bidirectional transport systems that are pivotal for renal pharmacokinetics, drug interactions and nephrotoxicity,
Drug Transport across the Blood-Brain Barrier and the in the Kidney

We are focusing on changes and signaling mechanisms of ABC-transporter-, tight junction- and receptor-expression and -function at the blood-brain barrier and in the kidney particularly occurring during Parkinson’s Disease (alpha-Synuclein) or the exposure towards environmental pollutants (Arylhydrocarbon-Receptor-dependent signaling), endocrine disrupters or oxidative stress (Nrf2) in in vitro, ex vivo and in vivo models (porcine brain capillary endothelial cells, isolated rat brain capillaries, human primary renal proximal epithelial tubule cells, isolated renal proximal tubules from killifish).

The major approach is to understand modifications and dynamic changes in blood-brain barrier permeability during CNS diseases and in the excretory capacity of the kidney evoked by xenobiotics. These insights could help to provide mechanisms of how to interfere with drug transporter signaling pathways in order to improve drug delivery into the brain and to explain alterations in renal drug elimination.
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Dr. Anne Mahringer studied pharmacy at the Ruprecht-Karls University of Heidelberg and obtained her PhD at the Institute of Pharmacy and Molecular Biotechnology at the Department of Pharmaceutical Technology and Biopharmaceutics under the professorship of Professor Dr. Gert Fricker. After several stays abroad at the NIEHS (National Institute of Environmental Health Sciences, North Carolina), the MDIBL (Mount Desert Island Biological Laboratory, Maine) and the Biomedical Center Uppsala (University Uppsala, Translational PKPD, Sweden) she is currently holding a postdoc position at the Institute of Pharmacy and Molecular Biotechnology at the Department of Pharmaceutical Technology and Biopharmaceutics in Heidelberg. Her research interests focus on drug transporter signaling at the blood-brain barrier and in the kidney as well as on endocytotic transport mechanisms of large peptides across the cerebrovascular endothelium.

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### Seminars, Lectures and Practical Courses

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