# The membrane transporters and their relevance in clinical Toxicology.

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Membrane transporters play a pivotal role in the absorption, distribution, metabolism, and excretion (ADME) of a wide range of endogenous and exogenous compounds. Their relevance in clinical toxicology has garnered significant attention due to their influence on drug efficacy, toxicity, and drug-drug interactions. This review explores the fundamental mechanisms of membrane transporters and their implications in clinical toxicology.

Membrane transporters are broadly classified into two superfamilies: the solute carrier (SLC) family and the ATP-binding cassette (ABC) family. SLC transporters, including organic anion transporting polypeptides (OATPs), organic cation transporters (OCTs), and organic anion transporters (OATs), facilitate the influx and efflux of various substances across cellular membranes. Conversely, ABC transporters, such as P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP), primarily mediate the efflux of substrates using ATP hydrolysis.

In clinical toxicology, the expression and function of these transporters can significantly impact the pharmacokinetics and toxicity profiles of therapeutic drugs and environmental toxins. Alterations in transporter activity, due to genetic polymorphisms, disease states, or co-administered drugs, can lead to variable drug responses and increased susceptibility to adverse effects. For instance, polymorphisms in the ABCB1 gene encoding P-gp have been associated with altered drug disposition and resistance, affecting the clinical outcomes of chemotherapeutic agents.

Furthermore, drug-induced transporter inhibition, induction or activation can result in significant drug-drug interactions, leading to either enhanced toxicity or therapeutic failure. The inhibition of renal transporters such as OAT1 and OAT3 by nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the renal clearance of methotrexate, resulting in severe toxicity. Similarly, the induction of hepatic transporters by rifampin can accelerate the clearance of co-administered drugs, necessitating dosage adjustments to maintain therapeutic efficacy. P-gp and BCRP at the BBB restrict the entry of potentially neurotoxic compounds into the central nervous system (CNS). However, dysfunction or inhibition of these transporters can increase CNS exposure to toxic substances, contributing to neurological adverse effects. Similarly, the induction and/or the activation of P-gp at intestinal and kidney level can reduce the absorption and increase the elimination, respectively, of toxics. Furthermore, drugs can be developed to induce and activate P-gp to be used as coadjuvant to reduce the adverse effects or nephrotoxicity of chemotherapeutics and antibiotics, substrates of P-gp.

Advances in transporter research have led to the development of experimental models to predict transporter-mediated drug interactions and toxicity. In this presentation, a compilation of in silico, in vitro, ex vivo, and in vivo studies developed by our research group will be discussed to demonstrate the relevance of modulating the P-gp efflux pump as a therapeutic approach. Specifically, by synthesizing and applying new molecules, we aim to reduce the intestinal and lung toxicity of the herbicide paraquat, increase neuroprotection against toxins at the BBB level, and reduce kidney exposure to nephrotoxic drugs.

In conclusion, membrane transporters are integral to the field of clinical toxicology, influencing drug disposition, toxicity, and interactions. A thorough understanding of transporter biology and its clinical implications is essential for improving drug safety and efficacy. The modulation of membrane transporters, particularly P-gp, through inhibition, induction, or activation can be an important strategy to mitigate the adverse effects or toxicity of drugs and toxins. Continued research in transporter pharmacogenomics, biomarker development, and predictive modeling will enhance our ability to manage and mitigate the toxicological risks associated with pharmacotherapy.