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Commentary

The Role of Drug Transporters in Tissue-Specific Drug Toxicity

Takumi Shugo*

Department of Pharmacokinetics, Tokyo University, Tokyo, Japan

ABOUT TO STUDY

Drug transporters play a critical role in determining the Absorption, Distribution, Metabolism, and Excretion (ADME) of pharmaceutical compounds. By mediating the movement of drugs across cellular membranes, these transporters significantly influence drug efficacy and toxicity. Tissue-specific drug toxicity often arises from the interactions between drugs and transporters in specific organs or cell types. Understanding these interactions can pave the way for developing safer and more effective therapeutic strategies. This article explores the mechanisms by which drug transporters contribute to tissue-specific drug toxicity, with a focus on key transporter families, their tissue distribution, and the implications of their activity in toxicity. We also discuss examples of drugs associated with transporter-mediated toxicity and strategies to mitigate these effects.

Tissue distribution of drug transporters

Drug transporters are differentially expressed in tissues, contributing to the tissue-specific effects of drugs. Below is an overview of transporter expression in key organs:

Liver: The liver is a primary site for drug metabolism and excretion. Transporters like OATP1B1, OATP1B3, and MRP2 mediate drug uptake and efflux, respectively. Dysfunction or inhibition of these transporters can lead to hepatotoxicity due to drug accumulation.

Kidney: The kidneys play a vital role in drug clearance. Transporters such as OAT1, OAT3, and OCT2 facilitate drug uptake in renal tubular cells. Excessive transporter-mediated uptake can result in nephrotoxicity, as seen with drugs like cisplatin.

Brain: The Blood-Brain Barrier (BBB) is equipped with P-gp and BCRP to limit the entry of potentially neurotoxic compounds. Inhibition of these transporters can increase Central Nervous System (CNS) drug levels, leading to neurotoxicity.

Intestine: P-gp and BCRP are highly expressed in the intestinal epithelium and regulate drug absorption. Modulation of these transporters can influence systemic drug exposure and local gastrointestinal toxicity.

Mechanisms of transporter-mediated tissue toxicity

Drug transporters can contribute to tissue-specific toxicity through several mechanisms are Transporter-mediated uptake can lead to high intracellular drug concentrations, resulting in cellular damage. For instance, OAT1 and OAT3 are implicated in the accumulation of nephrotoxic drugs like tenofovir. Inhibition of efflux transporters such as P-gp can lead to increased intracellular concentrations of toxic drugs. This is particularly significant in the BBB, where P-gp protects the brain from harmful substances. Drugs competing for the same transporter can lead to altered pharmacokinetics and toxicity. For example, co-administration of probenecid with methotrexate inhibits OAT1 and OAT3, increasing methotrexate toxicity. Polymorphisms in genes encoding drug transporters can affect their function and expression, leading to interindividual variability in drug toxicity. For instance, polymorphisms in SLCO1B1, which encodes OATP1B1, are linked to statin-induced myopathy. Cisplatin, a widely used chemotherapeutic agent, is taken up by renal tubular cells *via* OCT2. High intracellular concentrations of cisplatin lead to oxidative stress and kidney injury. Statins are transported into hepatocytes by OATP1B1. Polymorphisms in SLCO1B1 can reduce transporter activity, leading to elevated systemic statin levels and an increased risk of myopathy. Digoxin is a substrate of P-gp. Inhibition of P-gp at the BBB can result in excessive drug accumulation in the brain, causing neurotoxic effects. Tenofovir is transported into renal cells by OAT1 and OAT3. Prolonged exposure to high intracellular concentrations can lead to mitochondrial toxicity and renal dysfunction. Identifying genetic polymorphisms in drug transporters can help predict individual susceptibility to toxicity and guide drug selection and dosing. Co-administration of transporter inhibitors or inducers can modulate drug exposure in specific tissues. For example, probenecid is used to reduce renal toxicity by inhibiting OAT1 and OAT3. Designing drugs with reduced affinity for transporters involved in toxicity or using targeted drug delivery systems can minimize adverse effects. Monitoring plasma drug levels and adjusting doses

Correspondence to: Kimura Shugo, Department of Pharmacokinetics, Tokyo University, Tokyo, Japan; E-mail: takumishugo@dwc.ac.jp

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can help avoid toxic concentrations in susceptible tissues.

Strategies

Advancements in molecular biology and computational modeling continue to improve our understanding of drug transporter functions and their role in tissue-specific toxicity. Technologies such as organ-on-a-chip and in silico simulations offer promising platforms for predicting transporter-mediated toxicity during drug development. Additionally, integrating transporter data into personalized medicine approaches can enhance therapeutic safety and efficacy. Drug transporters play a pivotal role in mediating tissue-specific drug toxicity through their influence on drug distribution and intracellular accumulation. Understanding the interactions between drugs and transporters is crucial for identifying toxicity risks and developing strategies to mitigate adverse effects. As research in this field progresses, incorporating transporter knowledge into drug design and clinical practice will significantly enhance the safety and effectiveness of pharmacotherapy.