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Perspective

# The Role of Transport Proteins in Drug Absorption, Distribution and Elimination

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## INTRODUCTION

Transport proteins play a vital role in the Absorption, Distribution, Metabolism, and Excretion (ADME) of drugs, collectively referred to as drug disposition. These proteins facilitate the movement of drugs and their metabolites across cellular membranes, influencing drug bioavailability, efficacy, and toxicity. Understanding the mechanisms through which transport proteins operate is critical in pharmacology and drug development, as they directly affect how drugs are processed in the body and how they exert their therapeutic effects.

## DESCRIPTION

### Transport proteins

Transport proteins are specialized proteins that mediate the movement of ions, nutrients, and drugs across biological membranes. They are integral to cellular processes such as nutrient uptake, waste removal, and maintaining cellular homeostasis. In the context of pharmacology, transport proteins are crucial for controlling the distribution of drugs within the body, influencing their absorption into the bloodstream, their distribution to target organs, and their elimination through various routes, including the liver and kidneys.

Transport proteins can be broadly classified into two categories:

**Active transporters:** These require energy, usually in the form of ATP, to move substances against their concentration gradient. Active transport is essential for the movement of drugs into cells or across cellular membranes when the drug's concentration in the cell is lower than in the surrounding environment.

**Facilitated transporters:** These do not require energy and rely on concentration gradients to transport drugs. Facilitated diffusion allows drugs to move passively from regions of high concentration to low concentration, aligning with the laws of diffusion.

### Key transport proteins involved in drug disposition

Several families of transport proteins are involved in the ADME processes of drugs. The two major families include Solute Carrier (SLC) transporters and ATP-Binding Cassette (ABC) transporters.

**Solute Carrier (SLC) transporters**: SLC transporters are involved in the uptake of drugs into cells, tissues, and organs. They can be further classified based on their specific substrates and mechanisms of transport. Some well-known SLC transporters in drug disposition include:

- **Organic Anion Transporting Polypeptides (OATPs):** These transport proteins are expressed in tissues such as the liver, kidneys, and intestines. OATPs mediate the uptake of a wide range of drugs, including statins, antiviral drugs, and anticancer agents, into cells.
- **Organic Cation Transporters (OCTs):** OCTs are involved in the uptake of positively charged molecules, including drugs like metformin. These transporters are primarily expressed in the liver and kidneys, where they facilitate the renal elimination and hepatic uptake of many drugs.
- **Peptide Transporters (PEPTs):** These transport proteins are responsible for the uptake of small peptides and some peptide-like drugs. PEPTs play a role in the absorption of drugs such as Angiotensin-Converting Enzyme inhibitors (ACE inhibitors) and certain antibiotics.
- **Monocarboxylate Transporters (MCTs):** MCTs facilitate the uptake of lactate, pyruvate, and several drugs, including antiviral agents, into cells.

**ATP-Binding Cassette (ABC) transporters:** ABC transporters are primarily responsible for efflux of drugs out of cells, tissues, or organs, which can reduce drug absorption or promote drug elimination. These transporters use energy from ATP hydrolysis to transport drugs against concentration gradients. Key ABC transporters include:

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- **P-glycoprotein (P-gp):** P-gp, encoded by the ABCB1 gene, is one of the most studied ABC transporters. It is expressed in various tissues, including the intestine, liver, kidneys, and blood-brain barrier. P-gp actively transports drugs out of cells, limiting drug absorption and influencing drug resistance. For example, P-gp is implicated in reducing the effectiveness of cancer chemotherapy drugs by pumping them out of tumor cells.
- **Multidrug Resistance Proteins (MRPs):** MRPs, including MRP1 and MRP2, are involved in the efflux of a wide range of drugs, including chemotherapeutic agents, antihypertensive drugs, and bile acids. These transporters are found in organs like the liver, kidneys, and lungs, and they play a crucial role in drug excretion.
- **Breast Cancer Resistance Protein (BCRP):** BCRP, encoded by the *ABCG2* gene, is another critical efflux transporter. It is involved in limiting the absorption of drugs in the intestine and enhancing their elimination *via* the liver and kidneys. BCRP also plays a role in drug resistance in cancer, particularly to certain chemotherapeutic agents.

## Transport proteins in drug absorption

The absorption of orally administered drugs into the bloodstream occurs primarily in the gastrointestinal tract, where transport proteins mediate the movement of drugs across the intestinal epithelium. The efficiency of absorption can be influenced by the type and activity of transport proteins expressed in the gut.

For example, the OATP family of transporters facilitates the uptake of various drugs into intestinal cells, influencing their bioavailability. However, P-glycoprotein (P-gp) can limit drug absorption by pumping drugs back into the intestinal lumen, reducing their bioavailability. This interplay between uptake transporters and efflux transporters is crucial in determining the extent to which drugs enter the bloodstream after oral administration.

## Transport proteins in drug distribution

After absorption, drugs enter the bloodstream and are distributed to various tissues and organs. The distribution of drugs within the body is influenced by the action of transport proteins in cell membranes, particularly in organs like the liver, brain, and kidneys. For example, P-glycoprotein in the blood-brain barrier limits the entry of certain drugs into the Central Nervous System (CNS), which can affect the pharmacodynamics of drugs intended to treat neurological disorders.

In the liver, OATPs facilitate the uptake of drugs into hepatocytes for metabolism. In the kidneys, transport proteins like OCTs and MRPs play a role in the elimination of drugs by promoting their secretion into urine.

## Transport proteins in drug elimination

The kidneys and liver are the primary organs responsible for drug elimination. Transport proteins in these organs are involved in the renal excretion of drugs and their metabolites. In the kidneys, OCTs facilitate the uptake of drugs from the bloodstream into renal cells, while MRPs and P-gp contribute to the efflux of drugs into urine.

In the liver, drugs are often metabolized by enzymes, and the resulting metabolites are transported into bile by MRPs for excretion in the feces. Some transporters also contribute to the reabsorption of drugs in the kidneys, which can affect drug half-life and therapeutic efficacy.

## Clinical implications of transport proteins

The role of transport proteins in drug disposition has significant clinical implications. Variations in the expression and function of transport proteins can lead to differences in drug efficacy and toxicity among individuals. For example, genetic polymorphisms in P-glycoprotein can alter the absorption and distribution of drugs, influencing their therapeutic outcomes.

Furthermore, Drug-Drug Interactions (DDIs) can occur when one drug inhibits or induces the activity of transport proteins, leading to altered drug absorption, distribution, or elimination. For instance, certain drugs like grapefruit juice can inhibit P-glycoprotein, increasing the absorption of drugs that are substrates for this transporter, potentially leading to drug toxicity.

# CONCLUSION

Transport proteins are essential components of drug disposition, influencing how drugs are absorbed, distributed, metabolized, and excreted in the body. Understanding the role of transport proteins in drug pharmacokinetics is crucial for optimizing drug therapy, predicting drug interactions, and developing personalized treatments. As our understanding of transport proteins deepens, it will be possible to design drugs that better target specific transporters, improving both efficacy and safety profiles.