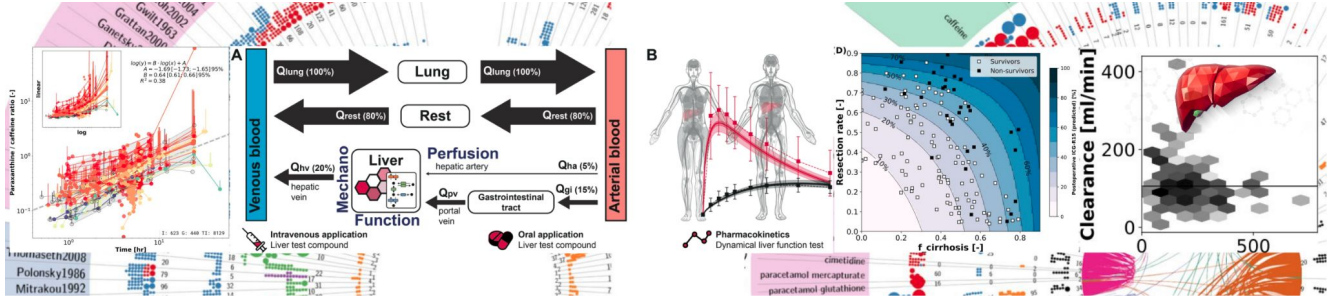

Pharmacokinetics Modeling Course

Metabolism

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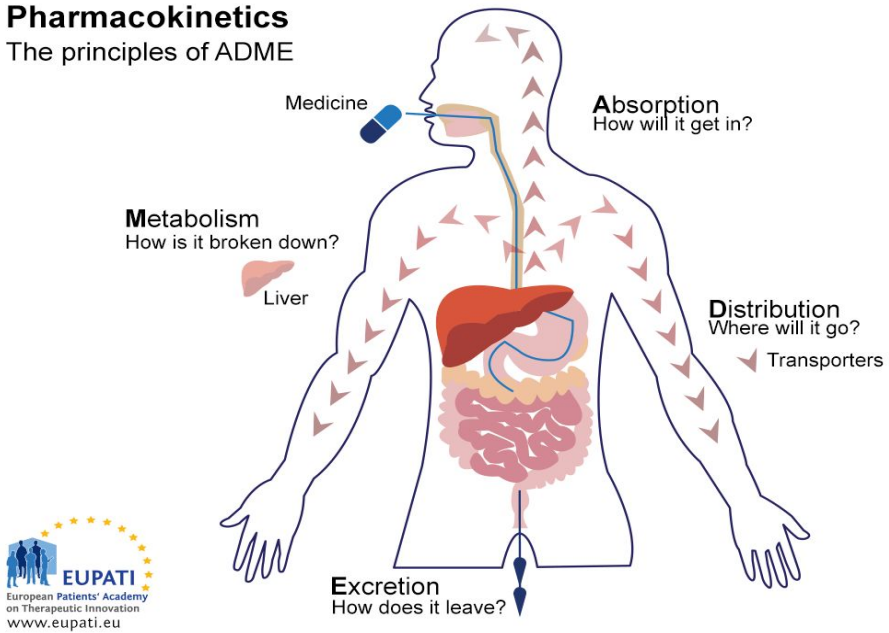
🎯 Teaching Goals

By the end of this section, you should be able to:

1. Provide an overview of **metabolic pathways** relevant to drug metabolism.
2. Understand **phase I and phase II metabolism** and their role in drug transformation.
3. Explain the concept of **prodrugs** and their activation via metabolism.
4. Recognize the **variability in enzyme expression** and the impact of **isoforms** (e.g., CYPs) on drug metabolism.
5. Describe **metabolic reaction kinetics** using **mass action**, **Michaelis-Menten**, and **Hill equations**.
6. Understand **enzyme inhibition and activation**, and how they affect drug clearance.
7. Explore **drug-drug interactions** mediated by metabolic pathways.

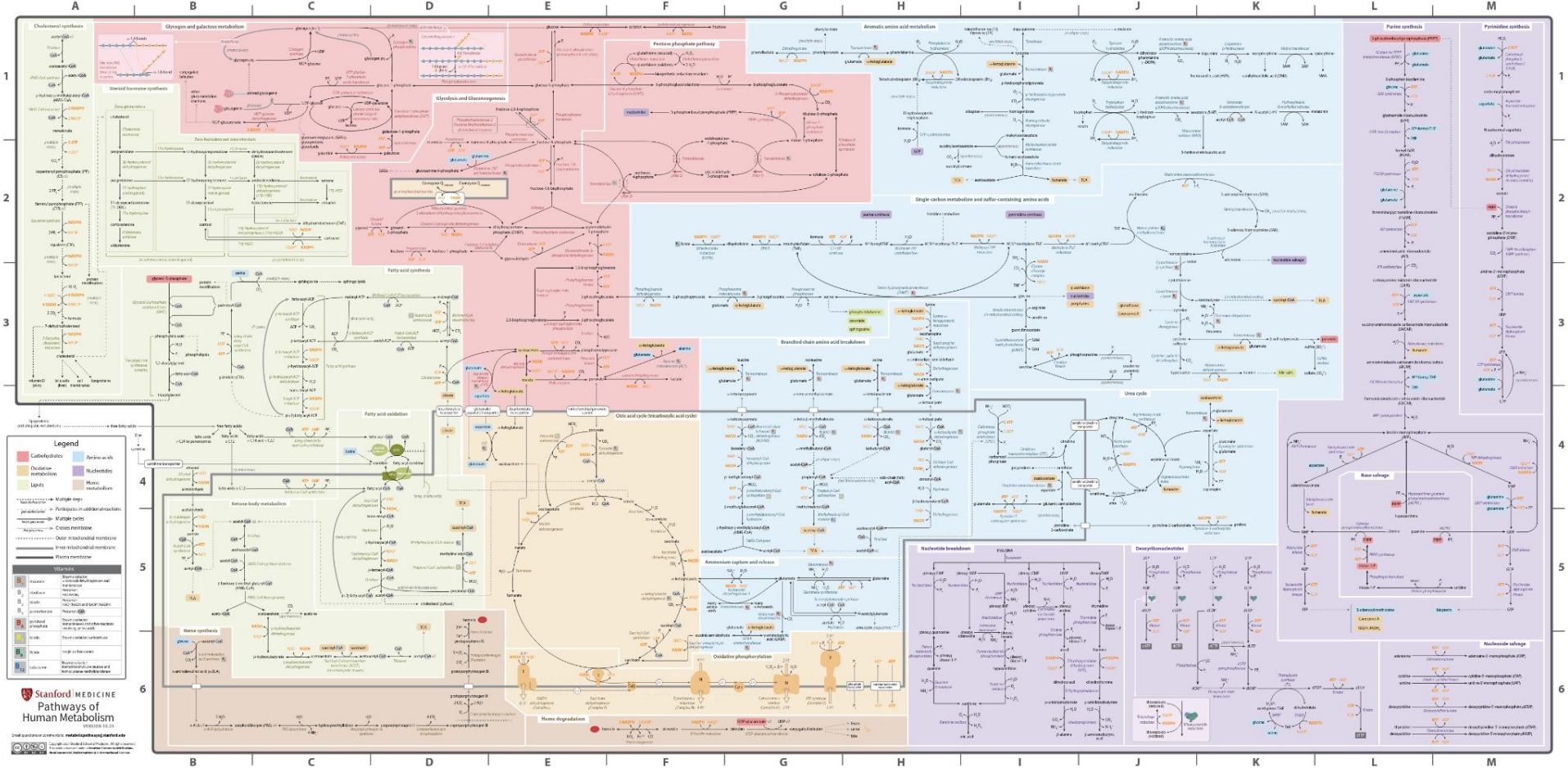
ADME



ADME processes determine pharmacokinetics

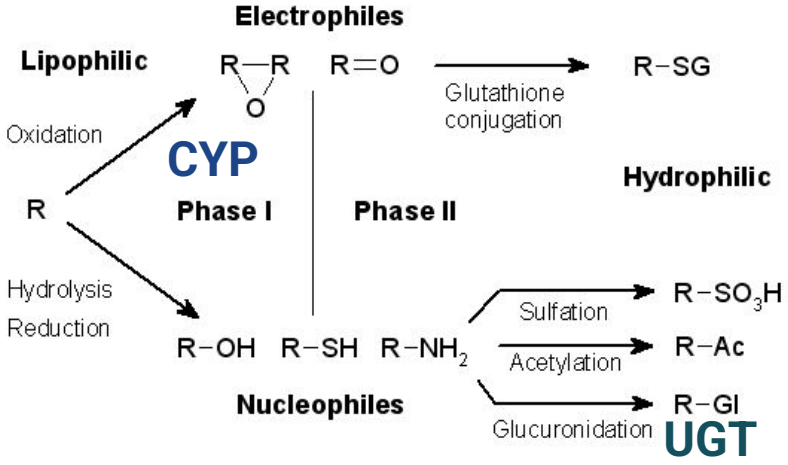
- **A**bsorption
- **D**istribution
- **M**etabolization
- **E**limination

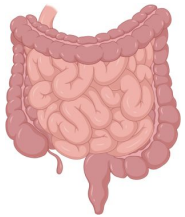
Stanford Pathways of Human Metabolism
https://metabolicpathways.stanford.edu/

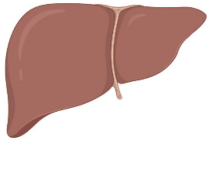


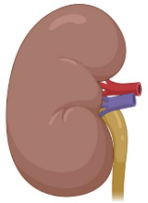
Drug Metabolism in a Nutshell

- Metabolism of xenobiotics is often divided into 3 phases: **modification, conjugation, and excretion**.
- **Cytochrome P450 (CYP)** main players in phase I (modification)
- **UDP-glucuronosyltransferases (UGT)** main players phase II (conjugation)
- **ATP-binding cassette (ABC)** and **Solute Carrier (SLC)** transporters are main drug transporters
- **Multiple isoforms** of CYP, UGT, ABC and SLC with different substrate specificity
- **Multiple organs**
  - **Intestine**: often metabolization during absorption
  - **Liver**: main organ of **drug metabolism**
  - **Kidneys:** minor metabolism & **excretion** of (modified) compounds in the urine









https://en.wikipedia.org/wiki/Drug_metabolism

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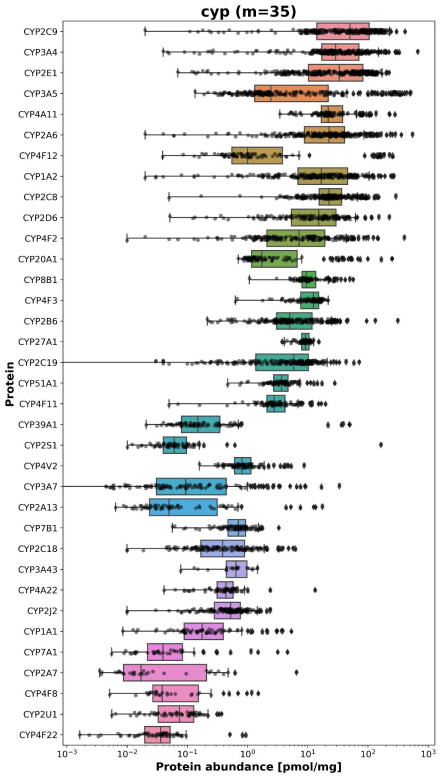
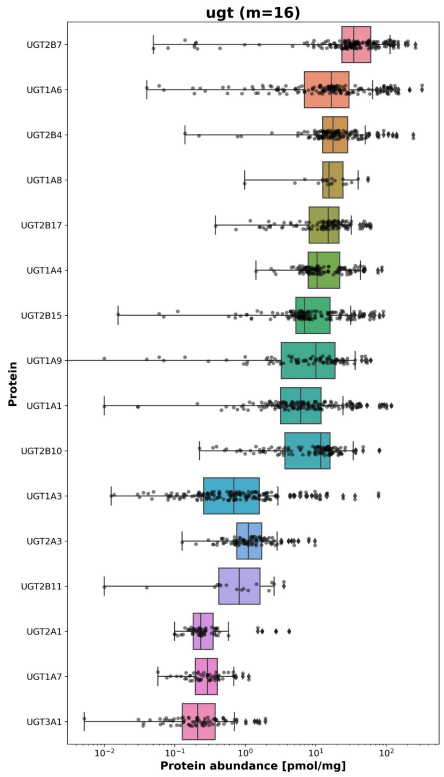
Large Variability & Multitude of Isoforms (Human Liver)

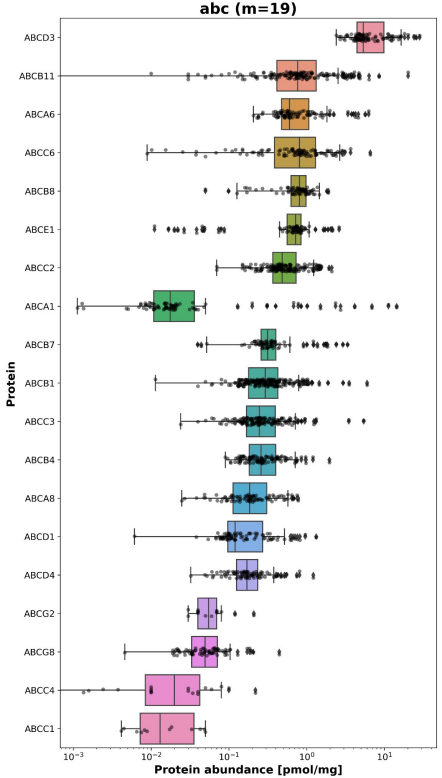
Cytochrome P450 (CYP)



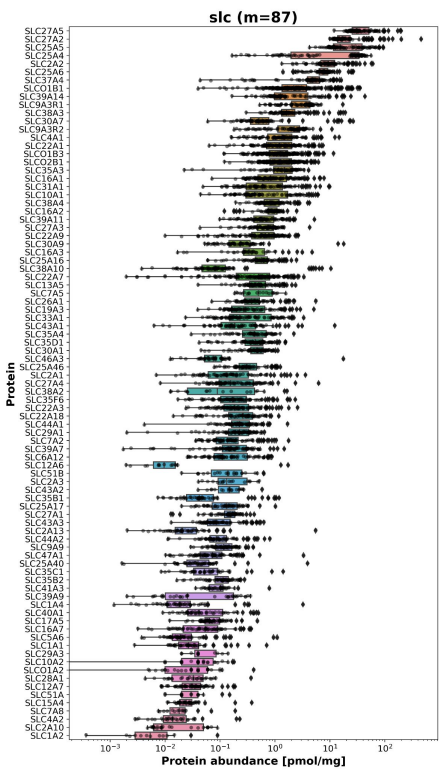
UDP-glucuronosyltransferases (UGT)



ATP-binding cassette (ABC)

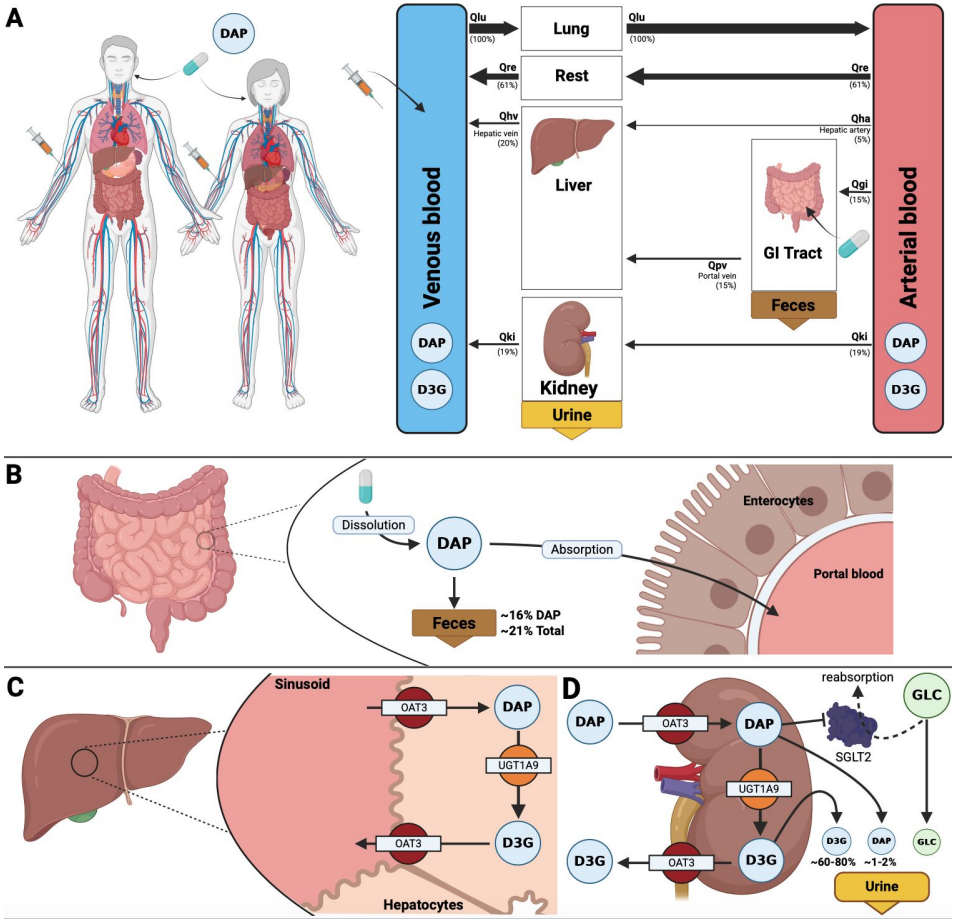


Solute Carrier (SLC)



Afruja Hossain, Sophie Silberhorn, Matthias König. **Protein distributions of drug metabolizing and transporting enzymes in the Human Liver.** In preparation.

Dapagliflozin Example (SGLT2 inhibitor)



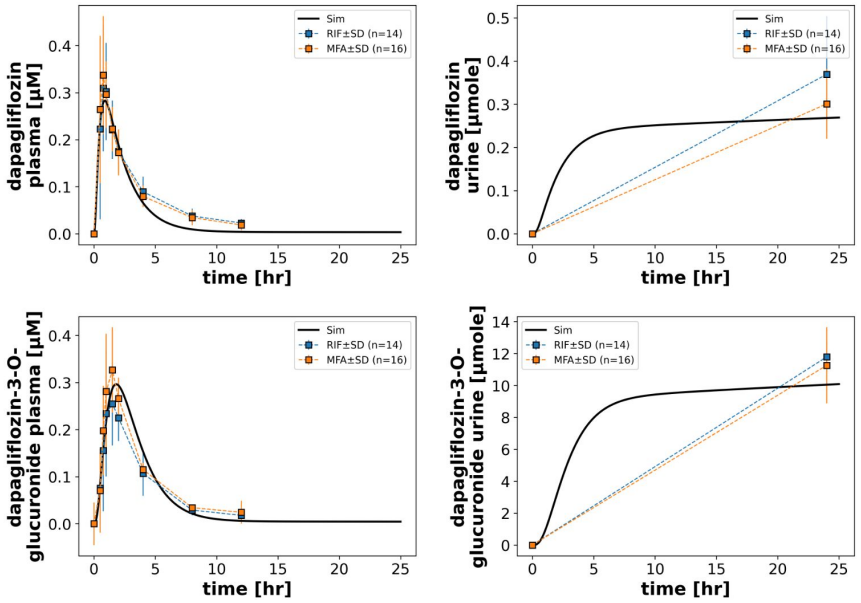


Figure 55: **Simulation of Kasichayanula et al. [27].**

Prodrugs

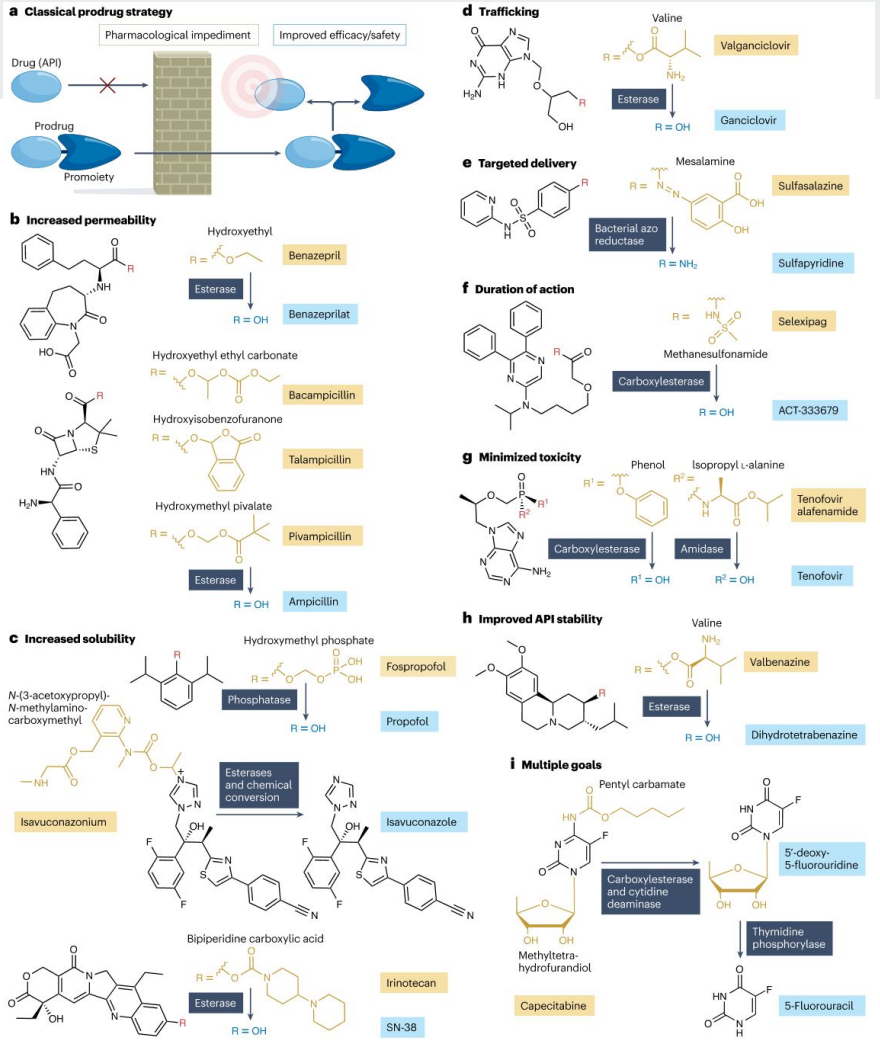
A **prodrug** is a pharmacologically inactive or less active compound that requires **metabolic conversion** to become therapeutically active.
Metabolic activation is usually carried out by **enzymes** in the **liver**, **intestine**, or **plasma** (e.g., esterases, cytochrome P450s).

Why use prodrugs?

- Improve **oral absorption** and **bioavailability**
- Enhance **tissue targeting**
- Reduce **side effects** or **toxicity**
- Overcome **formulation challenges**

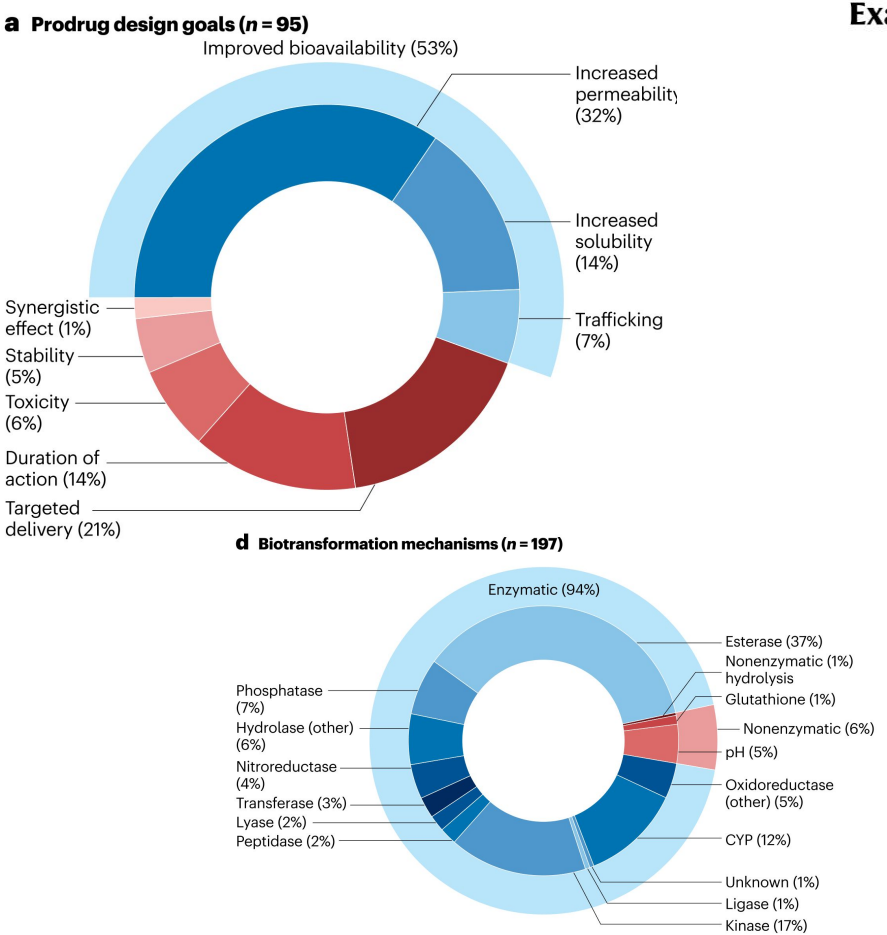
Clinical Examples:

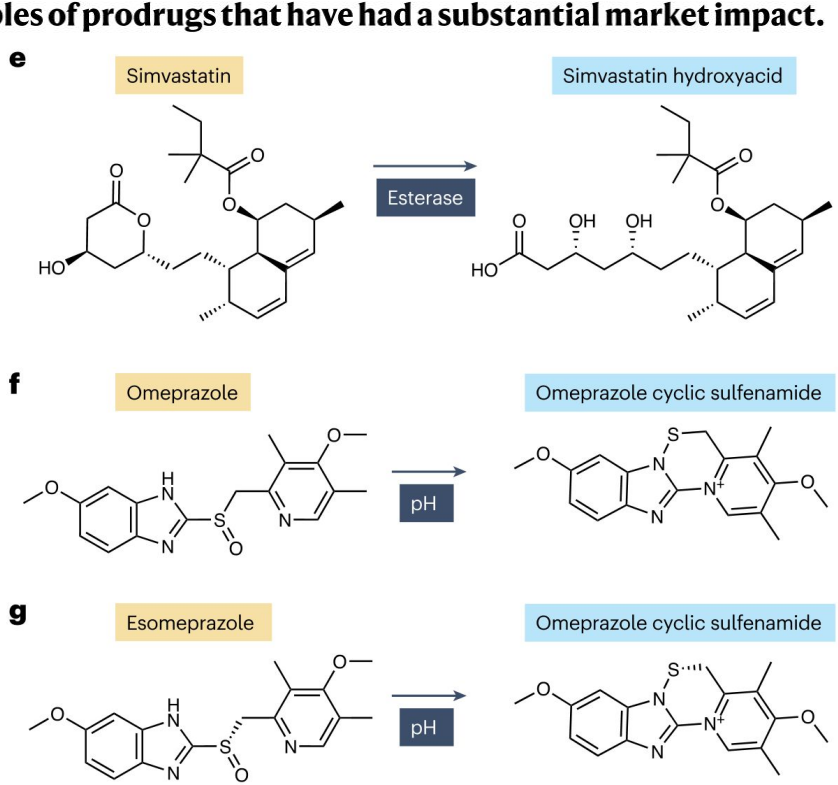
- **Enalapril** → Enalaprilat
- **Codeine** → Morphine
- **Clopidogrel** → Active thiol metabolite (via CYP2C19)



Fralish, Z., Chen, A., Khan, S. *et al.* The landscape of small-molecule prodrugs. *Nat Rev Drug Discov* **23**, 365–380 (2024). https://doi.org/10.1038/s41573-024-00914-7

Prodrugs & Metabolic Activation





Fralish, Z., Chen, A., Khan, S. *et al.* The landscape of small-molecule prodrugs. *Nat Rev Drug Discov* **23**, 365–380 (2024). https://doi.org/10.1038/s41573-024-00914-7

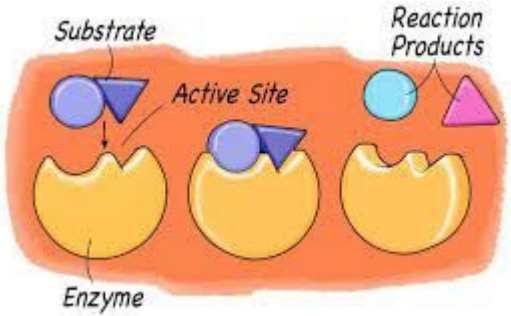
Metabolic Reaction Rates

In pharmacokinetics and enzymology, the rate at which reactions occur is crucial. Different mathematical models are used to describe these rates, with some of the most common being the Mass-Action model, the Michaelis-Menten model, and the Hill equation. Here's a brief summary of each:

1. Mass-Action Model: This model is one of the simplest and is based on the principle that the rate of a reaction is directly proportional to the concentration of the reacting substances. For a reaction A + B → C, the rate would be expressed as Rate = kAB, where k is the rate constant, and A and B are the concentrations of A and B.

2. Michaelis-Menten Model: This model is used to describe enzyme-catalyzed reactions, particularly when enzyme concentrations are much lower than substrate concentrations. Vmax is the maximum rate, A is the substrate concentration, and Km is the Michaelis constant (the substrate concentration at which the reaction rate is half of Vmax).

3. Hill Equation: This model is often used when there is cooperativity or interaction between multiple binding sites on a molecule (like a protein or enzyme). The Hill coefficient n represents the degree of cooperativity.



$$v = k \cdot A \cdot B$$

$$v = \frac{Vmax \cdot A}{Km + A}$$

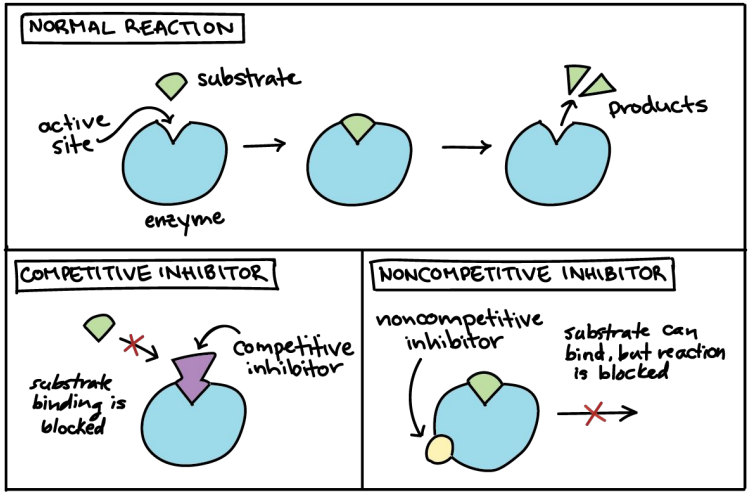
$$v = \frac{Vmax \cdot A^n}{Kd^n + A^n}$$

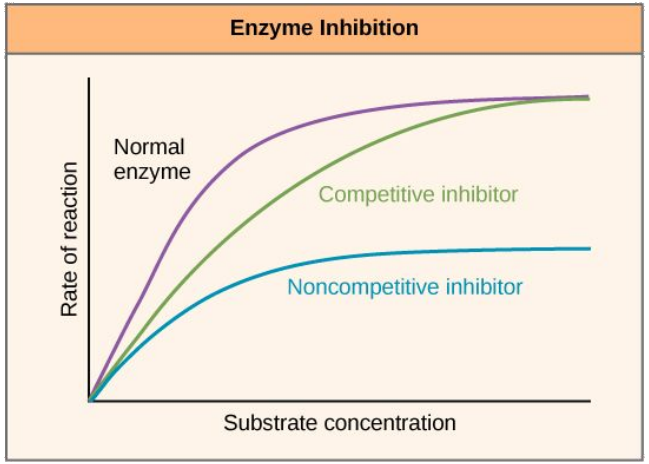
Inhibition & Activation

Inhibition and activation also play crucial roles in metabolic models:

- **Inhibition**: This occurs when a molecule binds to an enzyme and decreases its activity
  - **competitive** (bind to the active site and compete with the substrate)
  - **non-competitive** (bind to a separate site and change the enzyme's shape)
  - **uncompetitive** (bind to the enzyme-substrate complex).
  - Each type of inhibition changes the parameters (Vmax, Km) in distinctive ways.

- **Activation**: This is when a molecule binds to an enzyme and increases its activity. This can lead to an increase in the maximum reaction rate (Vmax) or a decrease in the Km value, indicating an increased affinity of the enzyme for its substrate.





https://www.khanacademy.org/science/ap-biology/cellular-energetics/environmental-impacts-on-enzyme-function/a/enzyme-regulation

Drug-Drug Interactions (DDI)

Drug-drug interactions (DDIs) occur when one drug affects the **pharmacokinetics or pharmacodynamics** of another, often via **metabolism**.

In metabolism, the most common mechanisms are:

- **Enzyme inhibition**: one drug **blocks** the enzyme that metabolizes another → **increased drug levels**, risk of **toxicity**
- **Enzyme induction**: one drug **increases** enzyme activity → **decreased drug levels**, risk of **therapeutic failure**

CYP450 enzymes, especially **CYP3A4**, **CYP2D6**, and **CYP2C9**, are frequent targets of metabolic DDIs.

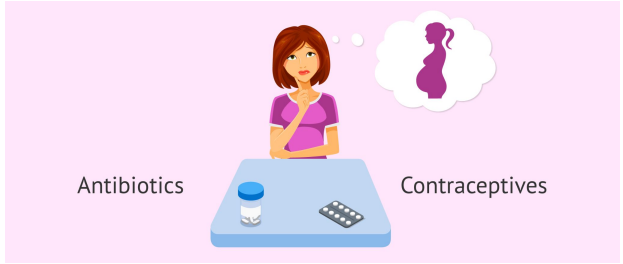
Examples:

- **Rifampin (inducer)** + **oral contraceptives** → contraceptive failure
- **Fluoxetine (inhibitor)** + **codeine** → reduced activation to morphine
- **Clarithromycin (inhibitor)** + **midazolam** → prolonged sedation

Table 2. **Common Drug Substrates, Inhibitors, and Inducers of CYP3A, According to Drug Class.***

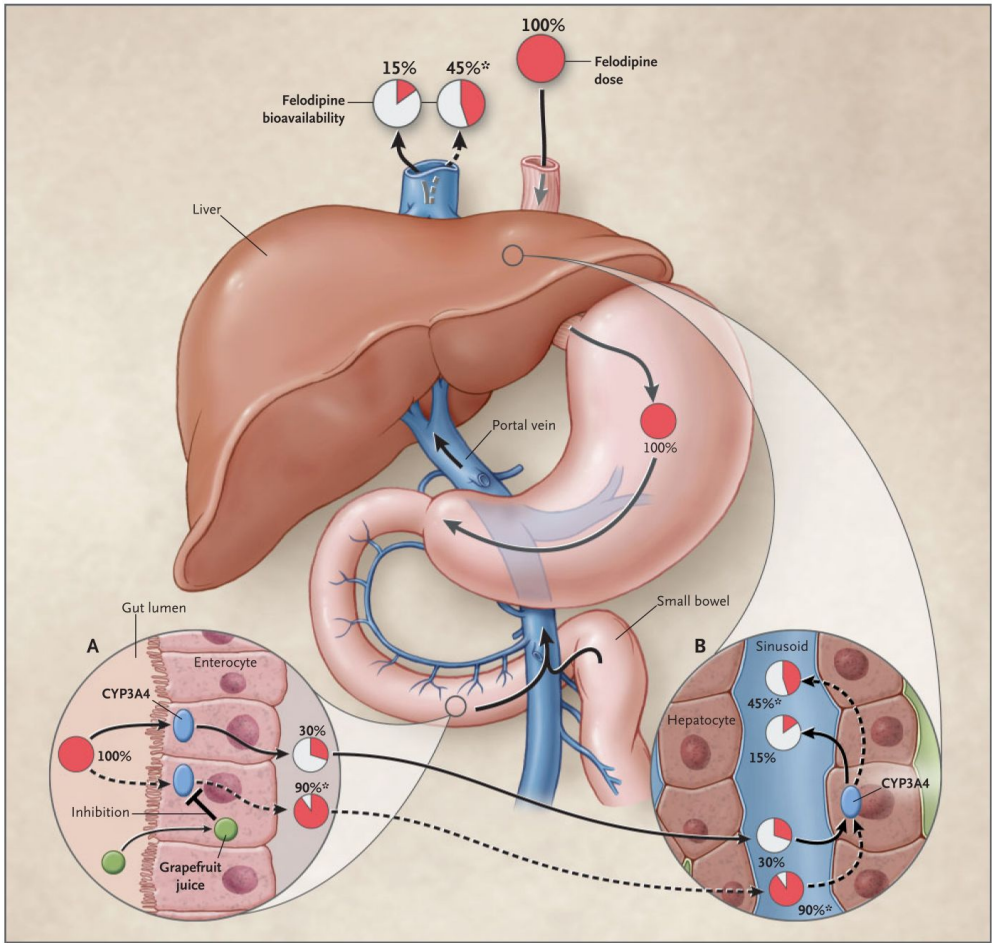
CYP3A Substrates	CYP3A Inhibitors	CYP3A Inducers
Calcium-channel blockers Diltiazem Felodipine Nifedipine Verapamil	Calcium-channel blockers Diltiazem Verapamil	Rifamycins Rifabutin Rifampin Rifapentine
Immunosuppressant agents Cyclosporine Tacrolimus	Azole antifungal agents Itraconazole Ketoconazole	Anticonvulsant agents Carbamazepine Phenobarbital Phenytoin
Benzodiazepines Alprazolam Midazolam Triazolam	Macrolide antibiotics Clarithromycin Erythromycin Troleandomycin (Not azithromycin)	Anti-HIV agents Efavirenz Nevirapine
Statins Atorvastatin Lovastatin (Not pravastatin)	Anti-HIV agents Delavirdine Indinavir Ritonavir Saquinavir	Others St. John's wort
Macrolide antibiotics Clarithromycin Erythromycin	Others Grapefruit juice Mifepristone Nefazodone	
Anti-HIV agents Indinavir Nelfinavir Ritonavir Saquinavir		
Others Losartan Sildenafil		

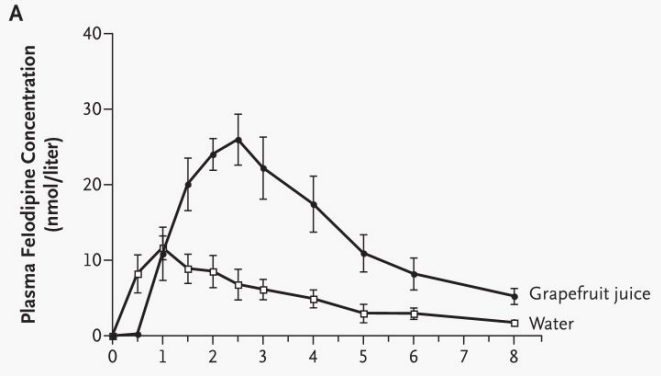
* These inhibitors and inducers can interact with any CYP3A substrate and may have important clinical consequences. HIV denotes human immunodeficiency virus.



Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005 May 26;352(21):2211-21. doi: 10.1056/NEJMra032424. PMID: 15917386.

Drug-Drug Interactions (DDI)





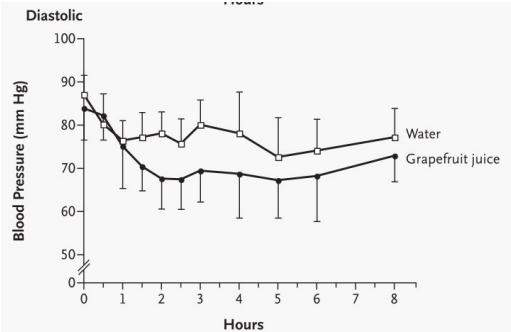
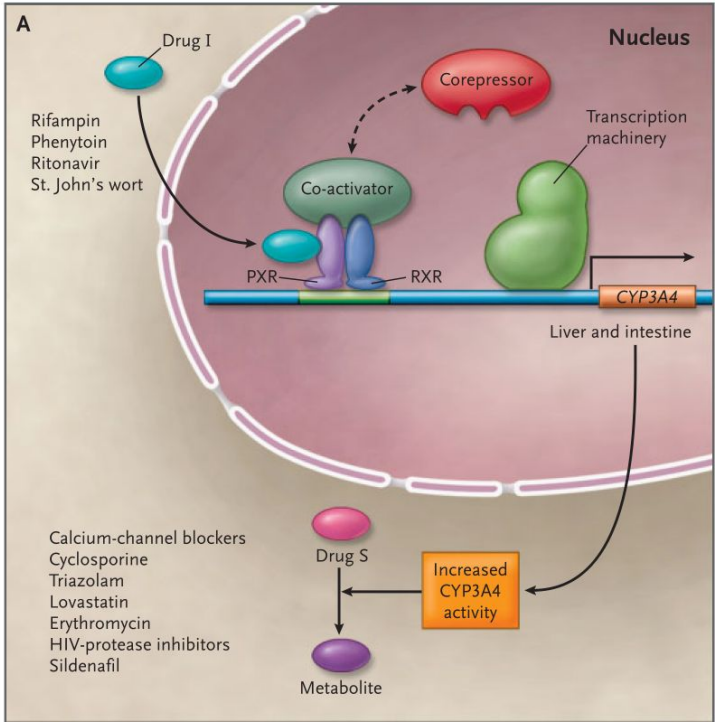


Figure 1. First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice.

CYP3A enzymes (e.g., CYP3A4) present in enterocytes of the intestinal epithelium extensively metabolize felodipine during its absorption, and on average only 30 percent of the administered dose enters the portal vein (solid line). Subsequently, CYP3A enzymes in the liver further metabolize the drug so that only 15 percent of the dose is bioavailable and finally reaches the systemic circulation and is able to exert its effects. Grapefruit juice selectively inhibits CYP3A in the enterocyte, with the net result being an increase in the oral bioavailability of felodipine by a factor of three, denoted by the asterisks and the dashed lines.

Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005 May 26;352(21):2211-21. doi: 10.1056/NEJMra032424. PMID: 15917386.

Drug-Drug Interactions (DDI)



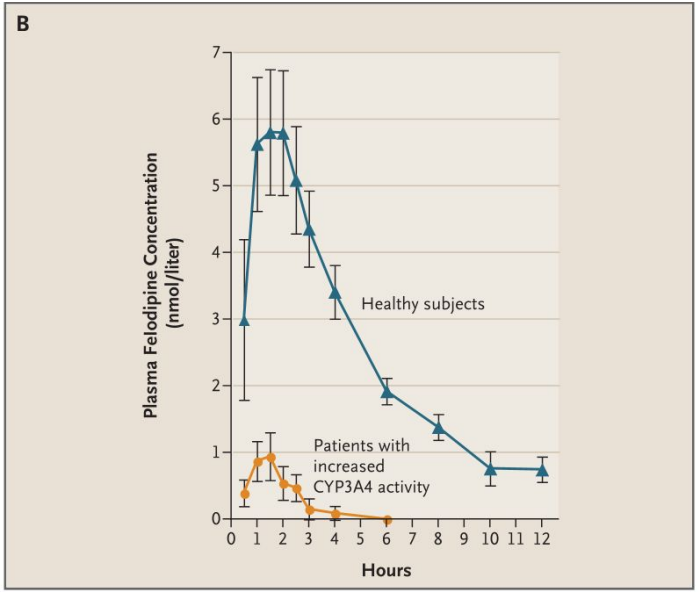
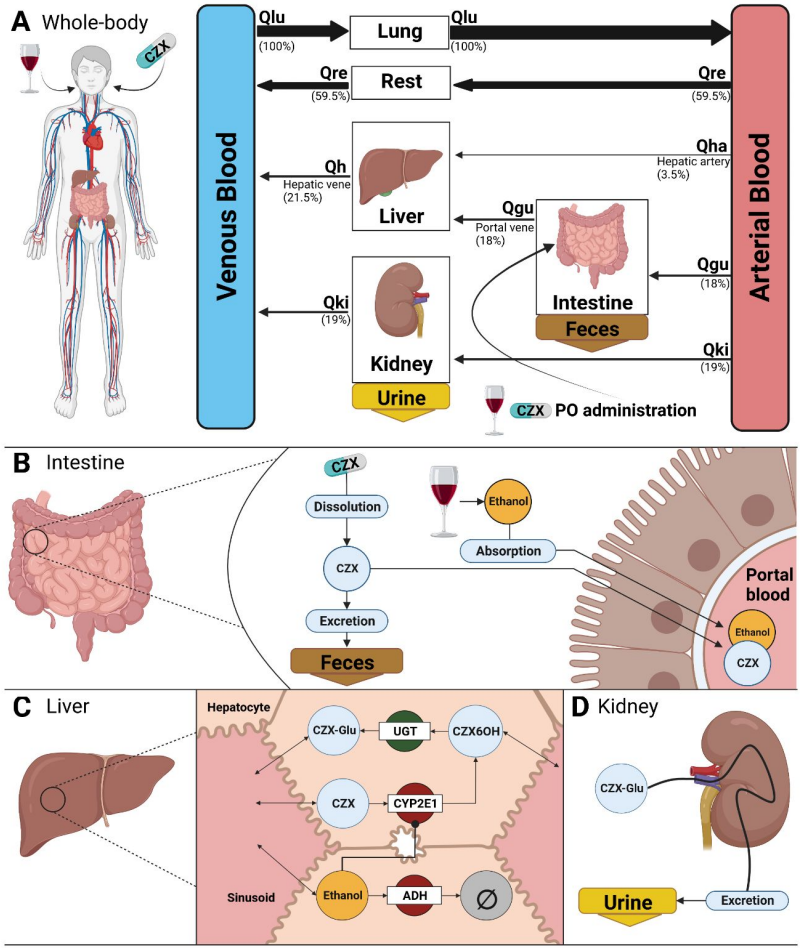


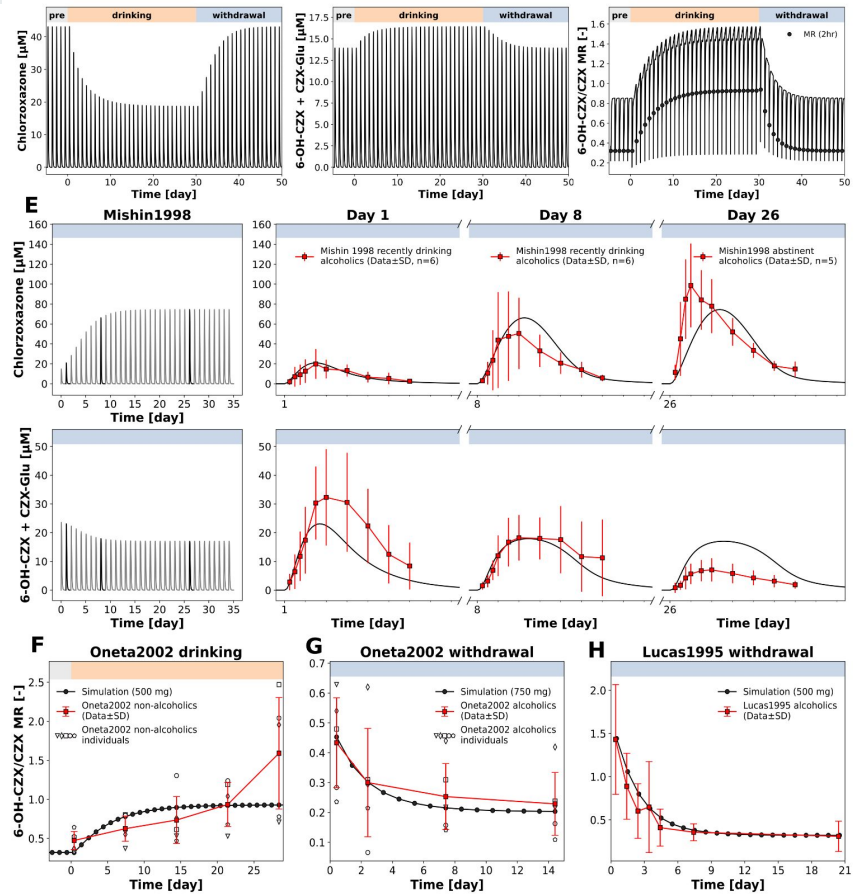
Figure 3. Mechanism of Induction of CYP3A4-Mediated Metabolism of Drug Substrates (Panel A) and the Resulting Reduced Plasma Drug Concentration (Panel B).

In Panel A, an inducing agent (Drug I) interacts with the nuclear receptor PXR (pregnane X receptor), which forms a heterodimer with the retinoid X receptor (RXR), which in turn binds to cognate recognition sites in the 5' regulatory region of the *CYP3A4* gene. As a result, transcription of DNA is up-regulated, leading to increased synthesis of CYP3A4 enzyme and enhanced oxidative metabolism of its substrates (Drug S). This causes a reduction in the plasma drug concentration as exemplified by felodipine (Panel B) and, subsequently, decreased drug effects. The same molecular mechanism is also responsible for the induction of other metabolizing enzymes and membrane transporters important in drug disposition. Comparison of the plasma felodipine concentration–time profiles in Panel B with those in Figure 2A indicates the wide range of CYP3A activity that is possible. I bars denote SEs. Panel B was adapted from Capewell et. al.,[8] with the permission of the publisher.

Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005 May 26;352(21):2211-21. doi: 10.1056/NEJMra032424. PMID: 15917386.

Alcohol induction CYP2E1 (chlorzoxazone)





A physiologically based pharmacokinetic model for CYP2E1 phenotyping via chlorzoxazone. J. Küttner, J. Grzegorzewski, HM. Tautenhahn, **M. König** bioRxiv 2023.04.12.536571 (preprint). doi:10.1101/2023.04.12.536571