Introduction to Pharmacology and Pharmacogenomics

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Pharmacogenomics

- Pharma = Drug
- Genomics/Genetics = study of genetic information
- Pharmacogenomics = study of how genetics/ genomics impacts drug phenotypes

What is a phenotype?

- Molecular: Gene products, protein structure
- Cell: Gene expression (ChIP-Seq, RNA-Seq)
- Organ: Liver metabolism of Drug X
- Organismal: Human metabolism of Drug X (liver + kidney)
- Clinical: Drug response (heart rate changes, liver enzyme panels, etc.)

Drug phenotypes

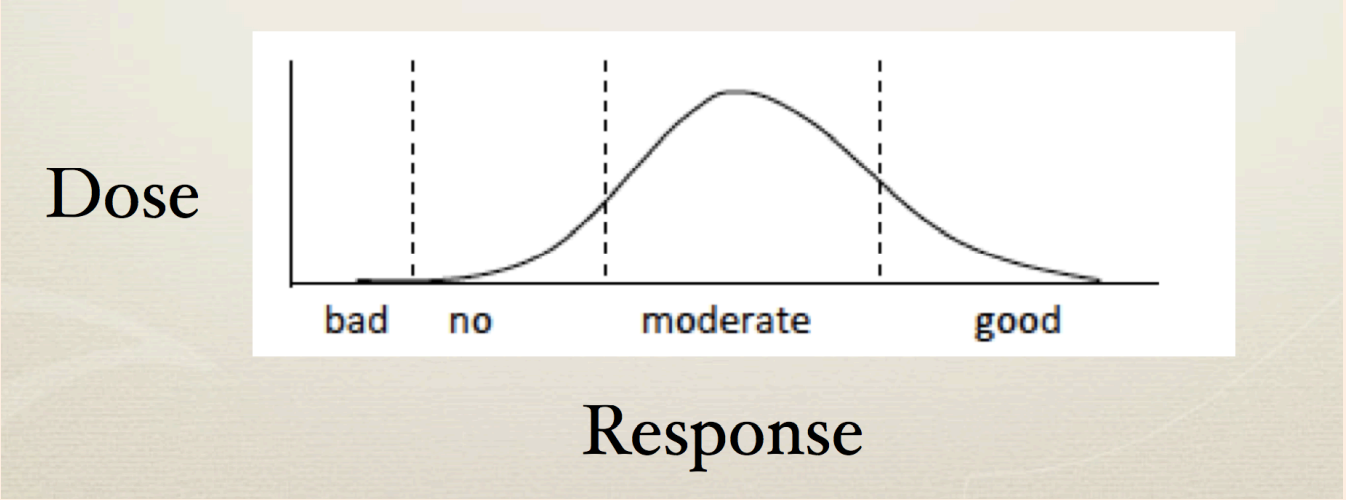
- Drug sensitivity – High dose or low dose needed to achieve the effect?
- Drug efficacy – Will the drug work for me?
- Adverse events – Will I experience unintended side effects/adverse events?

Genetics

- What is encoded in your DNA
  - Genotyping: Looking specifically in areas of known variation
  - Sequencing: Looking at the entire sequence (sequence a gene, exome, genome)

Why is pharmacogenomics important?

- 100,000 deaths/year due to medical error (most due to drugs)
- Drug dosing is “one size fits all”
- Pharmacogenomics can help differentiate between response groups and avoid adverse events



Drug sensitivity

- Do you think a loss of function mutation in a CYP enzyme leads to the need for a higher or lower dose?
- Answer: Either! Loss of function in CYP2C9 = can't metabolize warfarin to inactive product = more sensitive. Loss of function in CYP2C19 = can't metabolize clopidogrel into ACTIVE product, need higher dose

Adverse Effect (different from adverse event)

- An effect of a drug that is undesirable
  - Type A: Dose-related and predictable (on and off pathway side effects)
  - Type B: Idiosyncratic (off pathway side effect)

Type A Side Effects

Dose-related and predictable

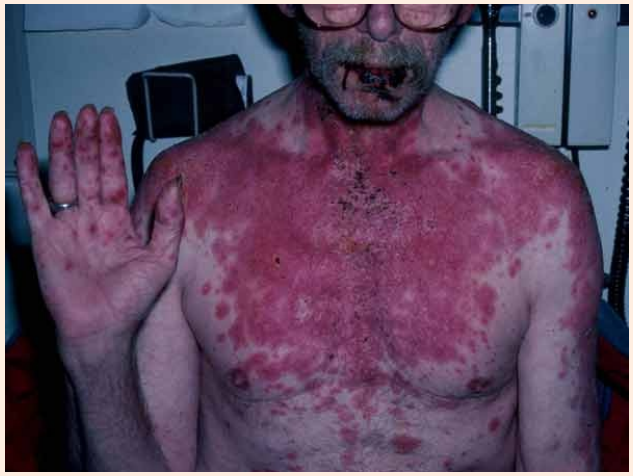
- Overdose of sleeping medication causes sleeping for too long
- Overdose can be virtual – due to your genetics – a normal dose is too much

Type B Side Effects

- Idiosyncratic (off pathway)
  - Tend to be rare (making it harder to study them)
  - Might not be dose-related (making them unpredictable)
  - Immune system is a large player in these effects
  - Immune system can produce a result unrelated to drug action

Adverse event

- Classified based on an outcome
- Death or hospitalization
- With pharmacogenomics, can be due to variants in pharmacokinetic, pharmacodynamic, or off pathway genes (immune)
- Common examples:
  - Liver toxicity (immune mediated)
  - Severe dermatological events (rashes, exfoliation)

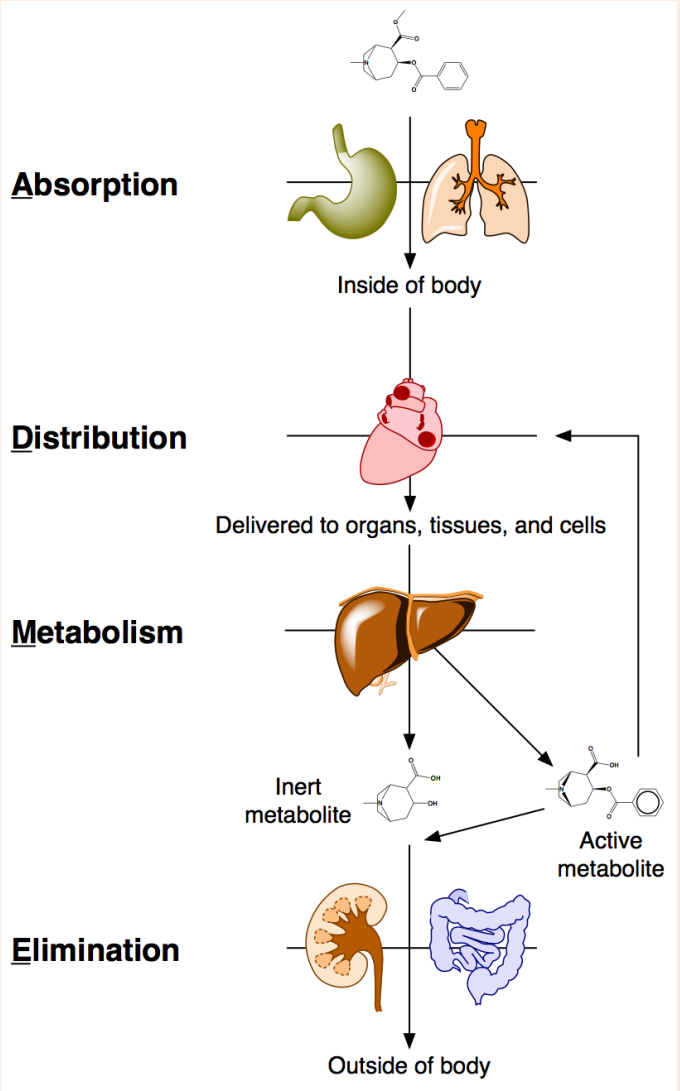


Pharmacology terms

- Pharmacokinetics (PK)
  - Getting the drug through the body
- Pharmacodynamics (PD)
  - Action (effects, good, or bad) of the drug

Pharmacokinetics
"What the body does to the drug"

- "ADME"
  - Absorption
  - Distribution
  - Metabolism
  - Elimination



Pharmacokinetics
"What the body does to the drug"

- Absorption: How the drug gets to the blood stream
  - Ingest a pill -> Digestive system
- What other mechanisms of absorption can you think of?
- For drugs absorbed through the digestive system, what factors affect absorption?

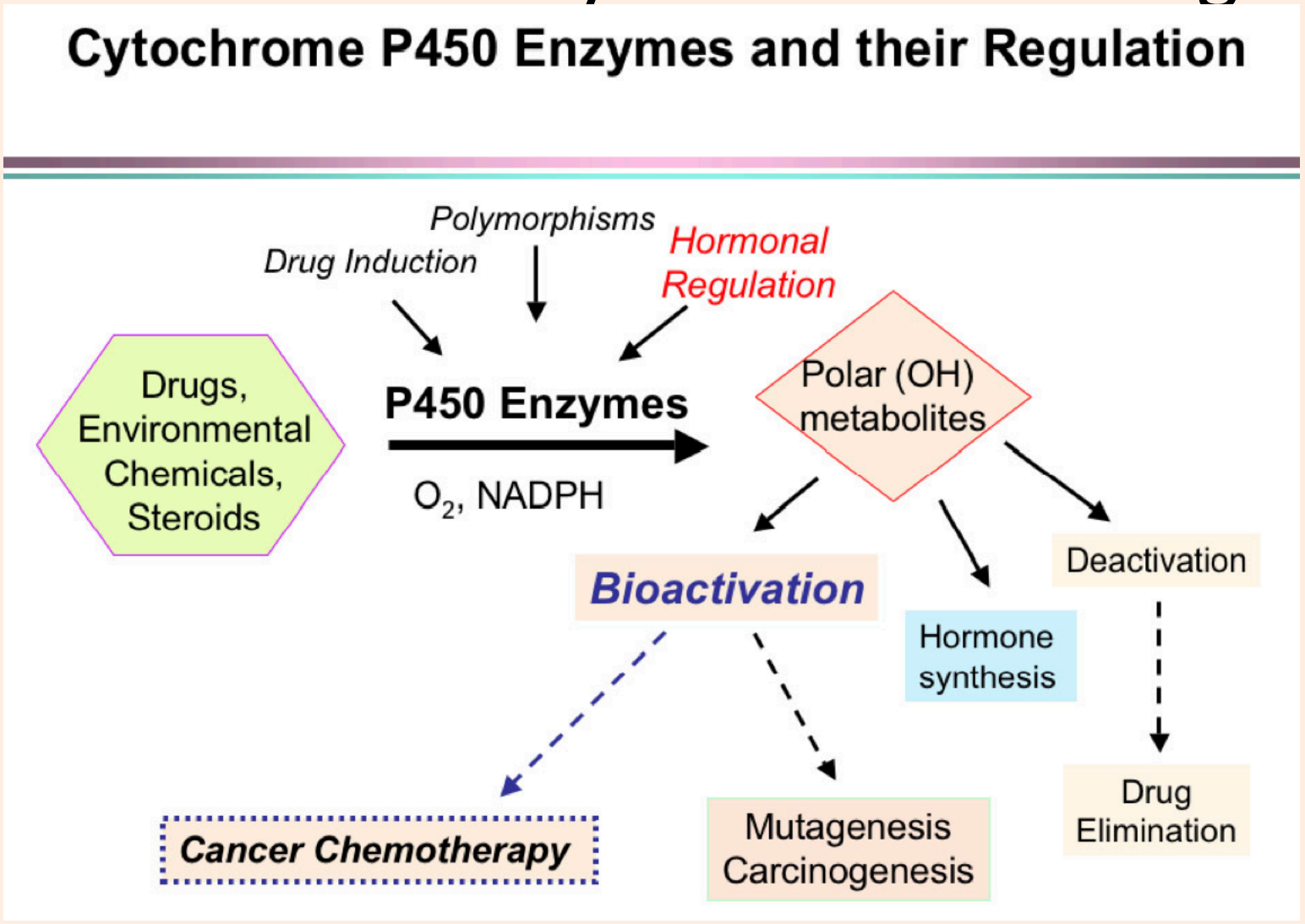
Pharmacokinetics
"What the body does to the drug"

- Distribution: Movement of the drug to and from the blood to other tissues of the body
- What tissues do you think it might move to?
- What factors affect distribution?

Pharmacokinetics
"What the body does to the drug"

- Metabolism: Altering the drug (into "metabolites")
  - Happens through redox reactions (enzymes known as p450 enzymes)
  - Sometimes, a metabolite is more active than the parent drug (example: codeine to morphine)

Pharmacokinetics
"What the body does to the drug"

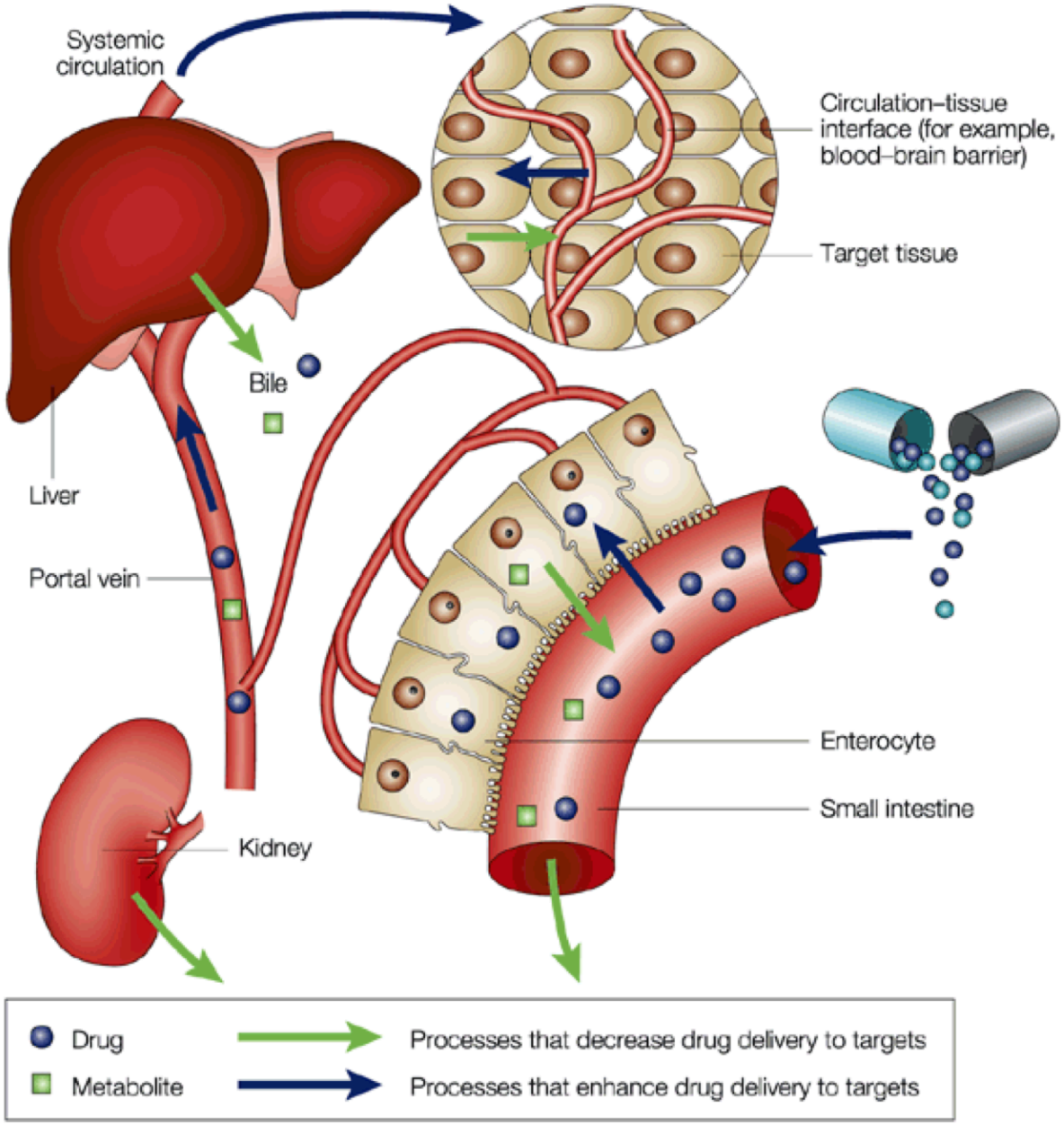


P450 enzymes: protecting us from our environment

- P450 enzymes did not evolve to deal specifically with drugs, but any set of xenobiotic insults we might encounter
- A uniquely human system (which makes animal testing of drugs difficult)
- Solution: A mouse with a human liver? (Gary Peltz at Stanford)

Pharmacokinetics
"What the body does to the drug"

- Elimination/Excretion: Drug and metabolites removed from the body
  - Mostly through feces (secreted with bile) and kidneys: Poop it out or Pee it out!
  - Anesthetics: Can also exhale it



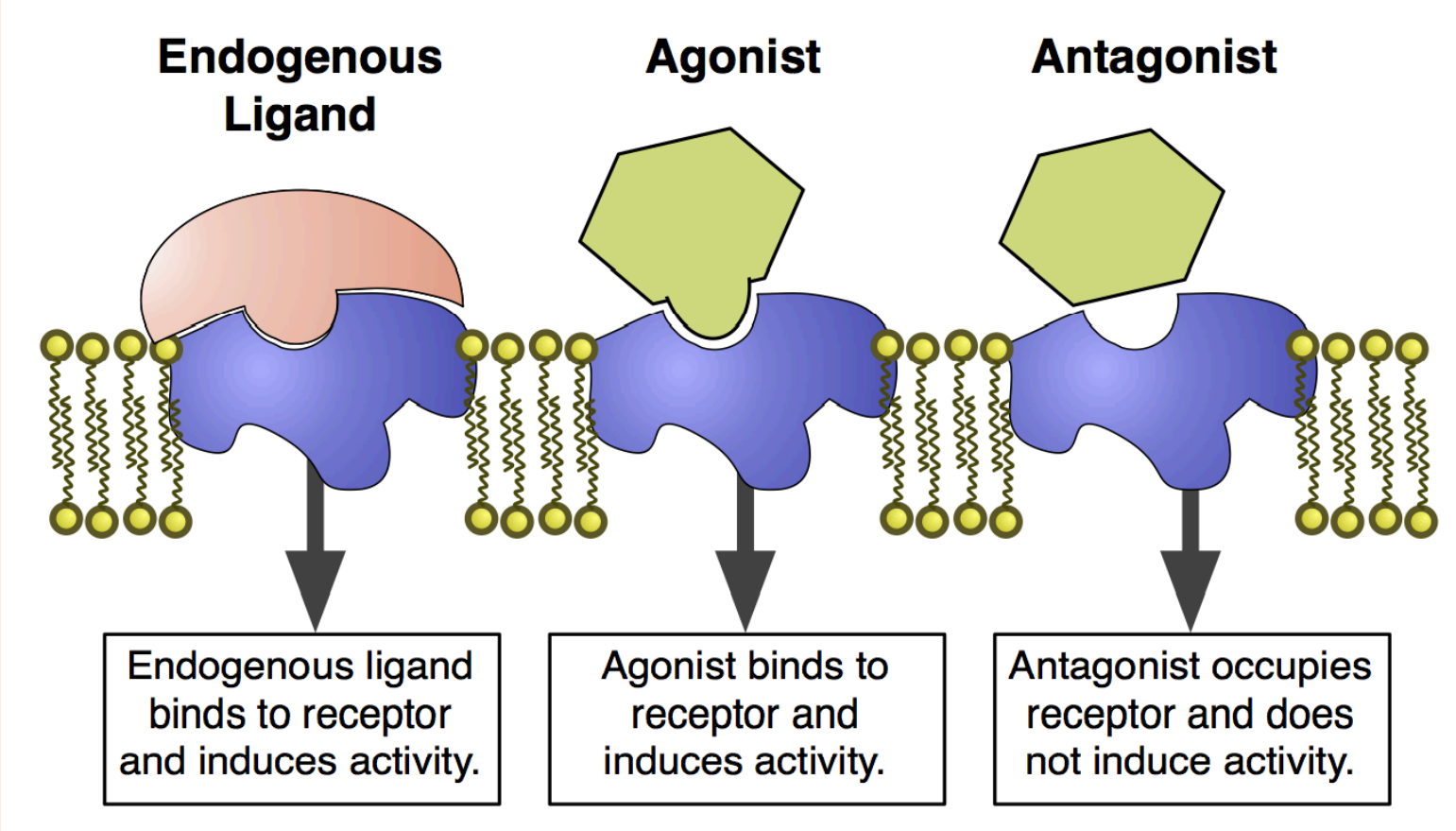
Roden et al., 2002

Pharmacodynamics
"What the drug does to the body"

- How the drug acts on the body
  - Target
  - Mechanism of Action
  - Drug Response

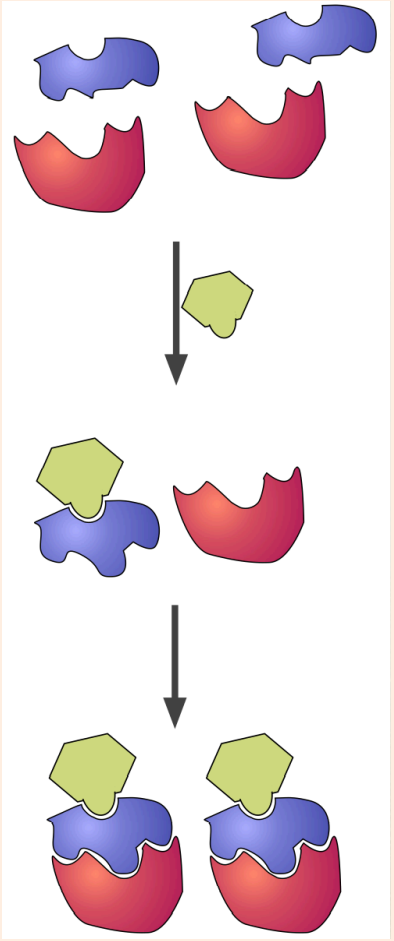
Pharmacodynamics
"What the drug does to the body"

Drug targets: agonists and antagonists



Pharmacodynamics
"What the drug does to the body"

- Mechanism of action
  - Drug binds to protein
  - Protein produces direct or indirect effect
  - Phenotype

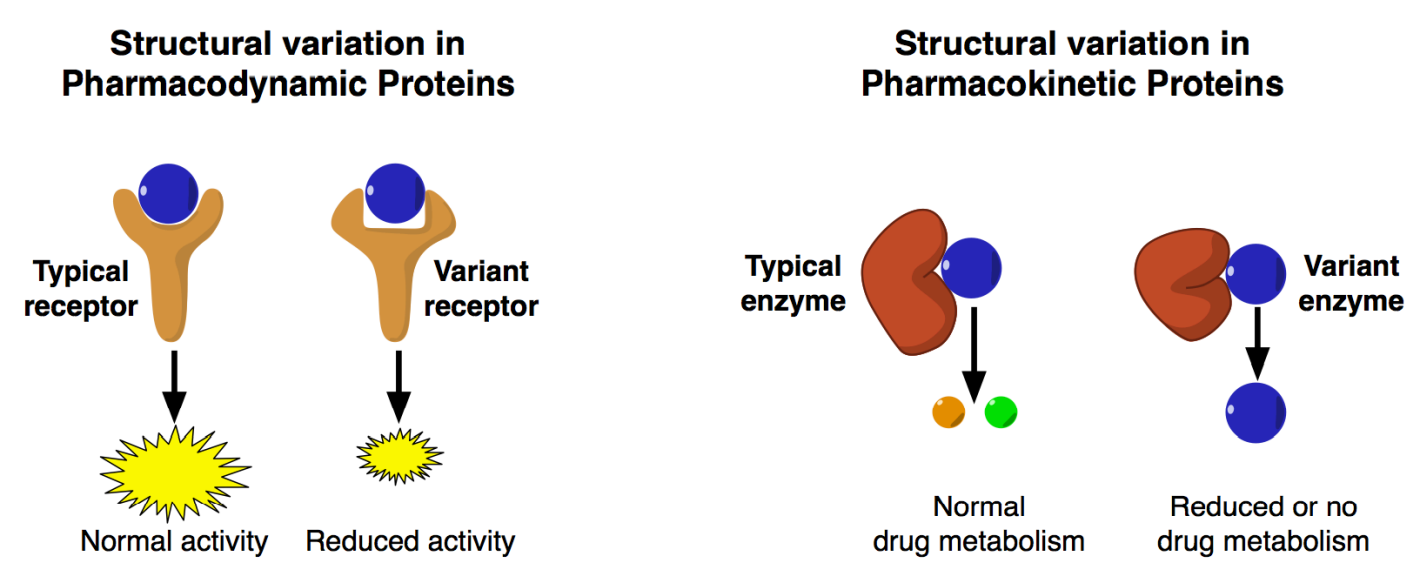


Drug Targets (examples)

- Enzymes (aromatase inhibitors, acetaminophen – blocks cyclooxygenases)
- Substrates, metabolites, proteins (Rasburicase acts on urate for those with tumor lysis syndrome)
- Receptors (Caffeine acts on G-protein-coupled adenosine receptors, estrogens act on nuclear/steroid receptors)
- Ion channels (Amiodarone blocks voltage-gated Potassium channels)
- Transporters (Omeprazole blocks H+/K+-ATPase)
- DNA/RNA and ribosome (Cisplatin crosslinks DNA)

Genetics can affect personal drug response

- Change in PD proteins -> change in activity of the drug
- Change in PK proteins -> change in amount of drug



Pharmacogenomics: Big picture