

**The fate of the drug in the body – why it is important? (ADME)**

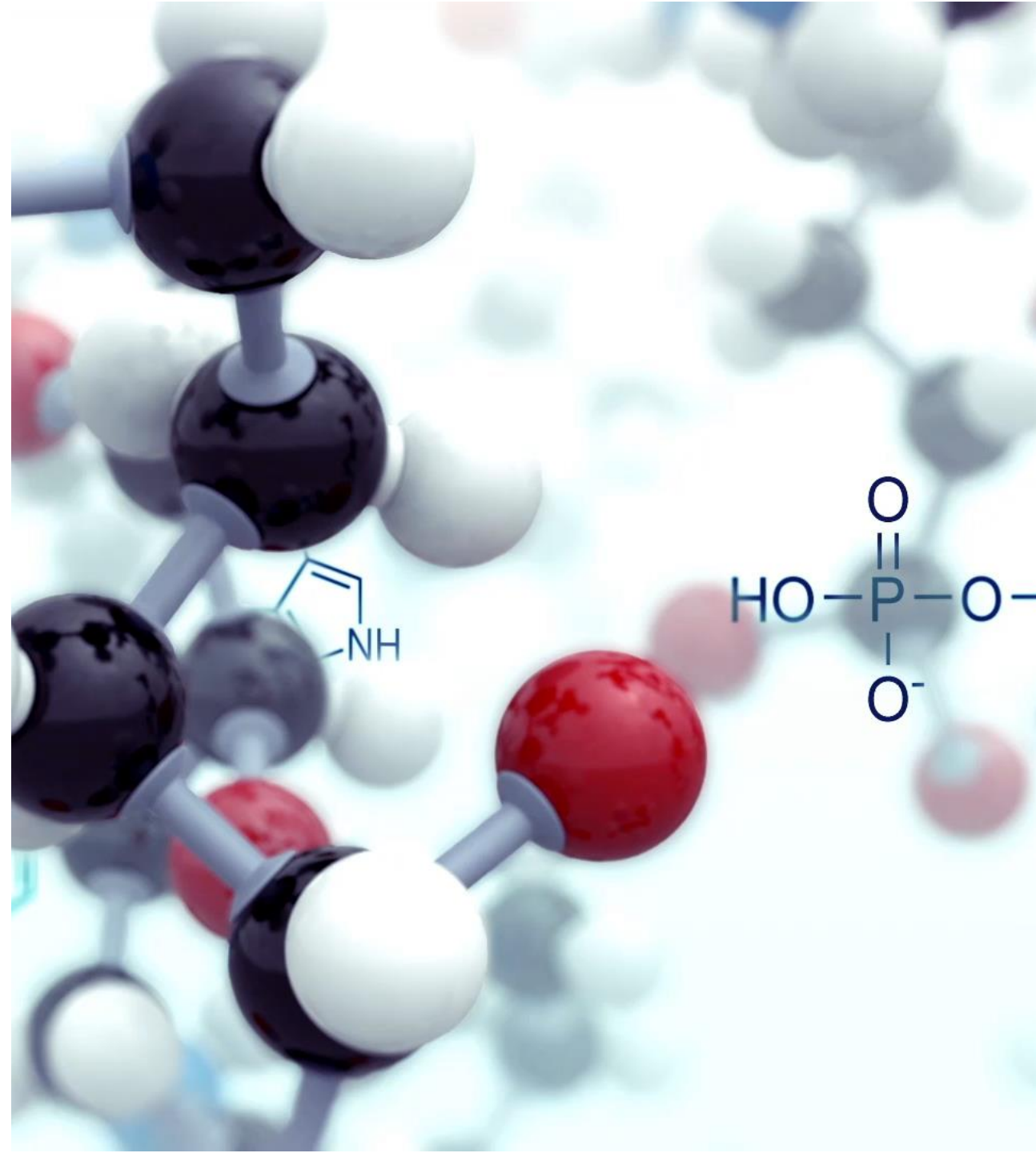
**Is the design of the medicines important?**



RNDr. Eva Havránková, Ph.D.

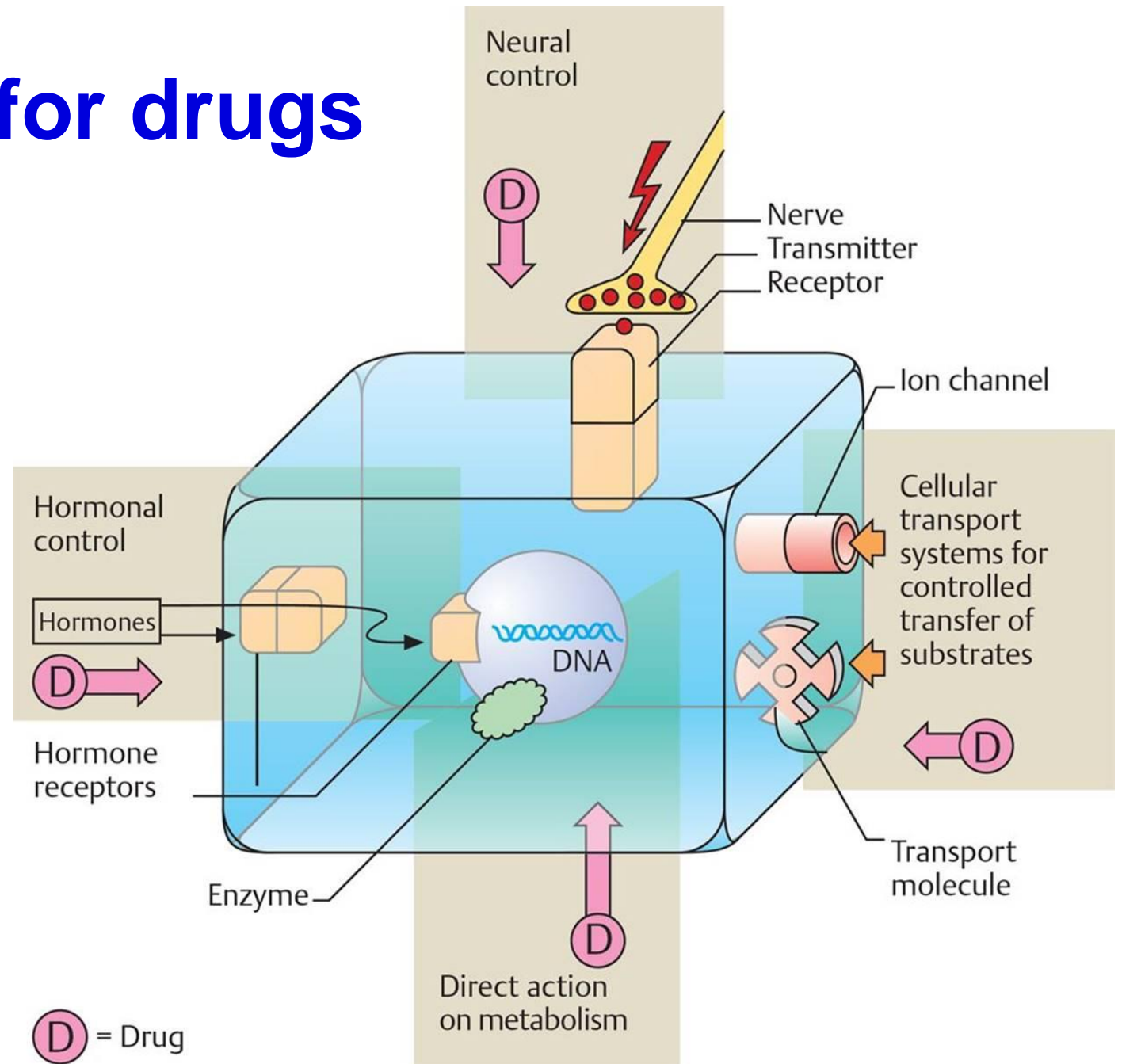
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# Mechanism of action

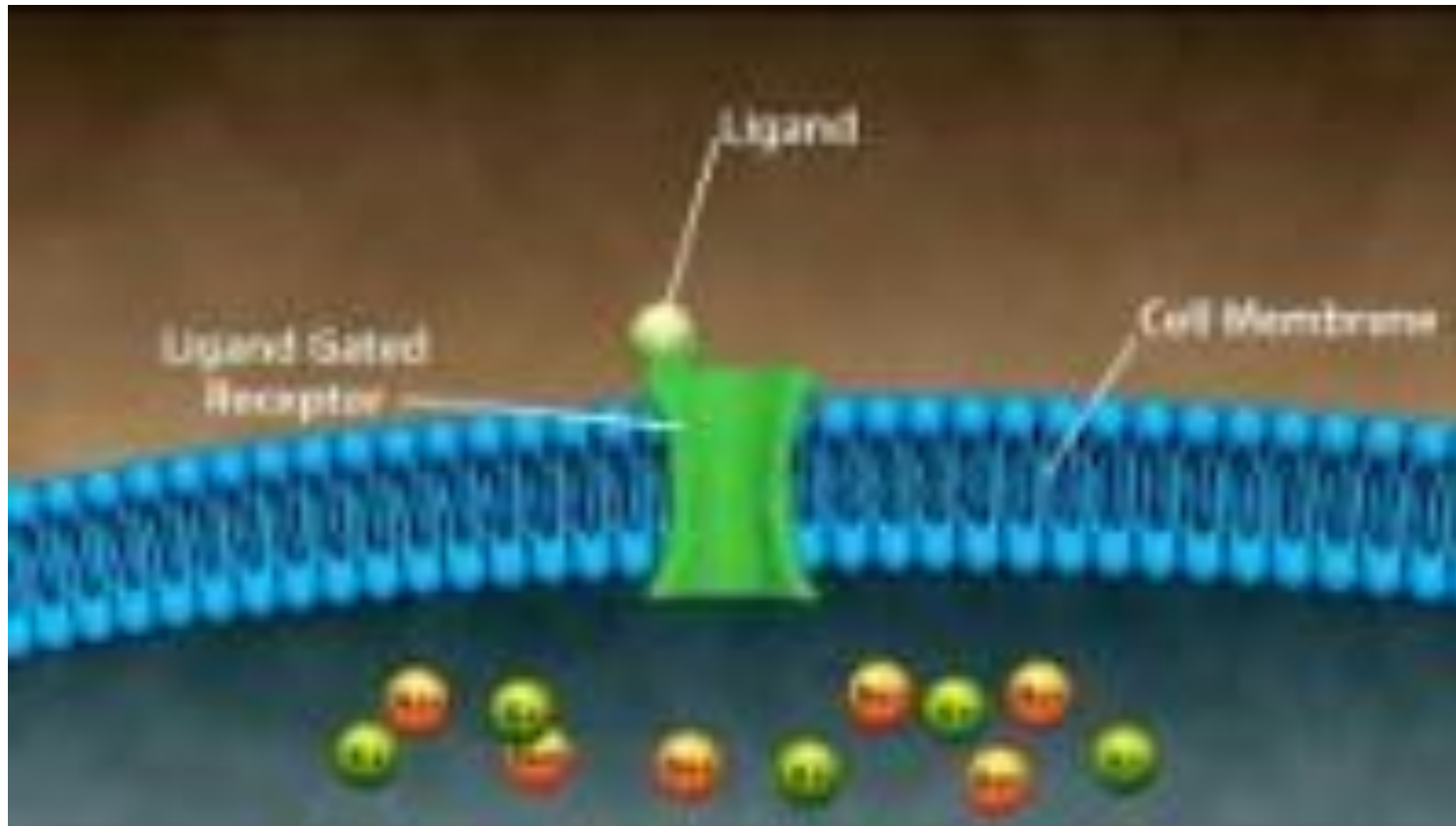


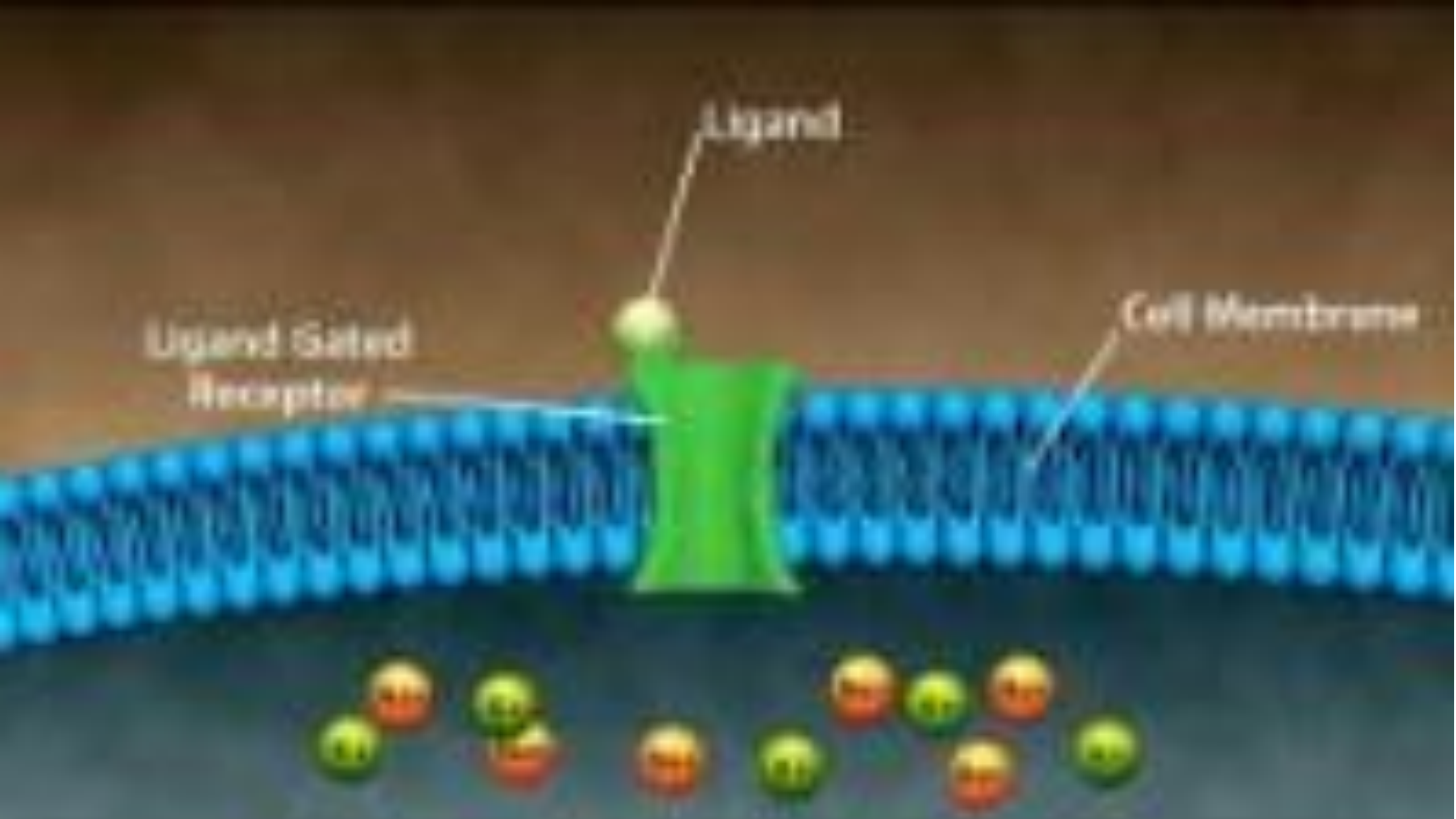
# Target structures for drugs

- Enzymes
- Receptors
- Transporters
- Channels
- DNA
- mRNA
- and more



# Most common targets for drugs

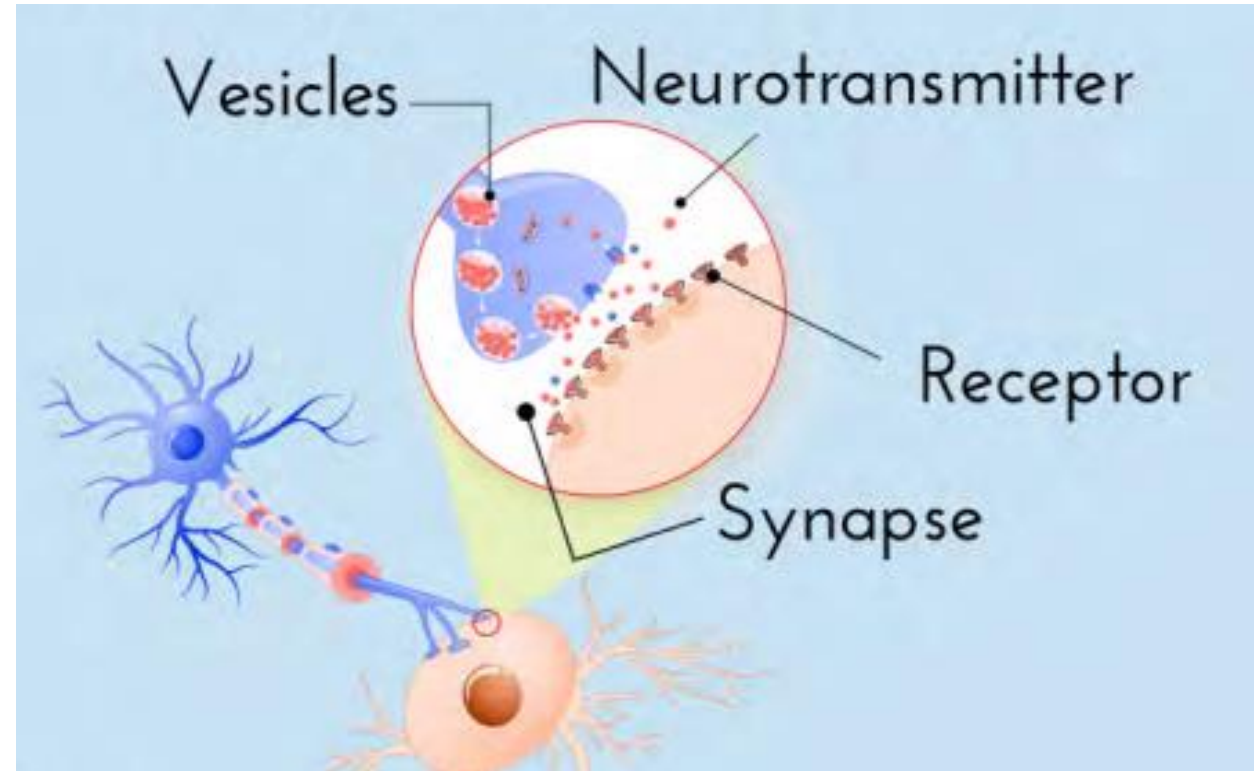


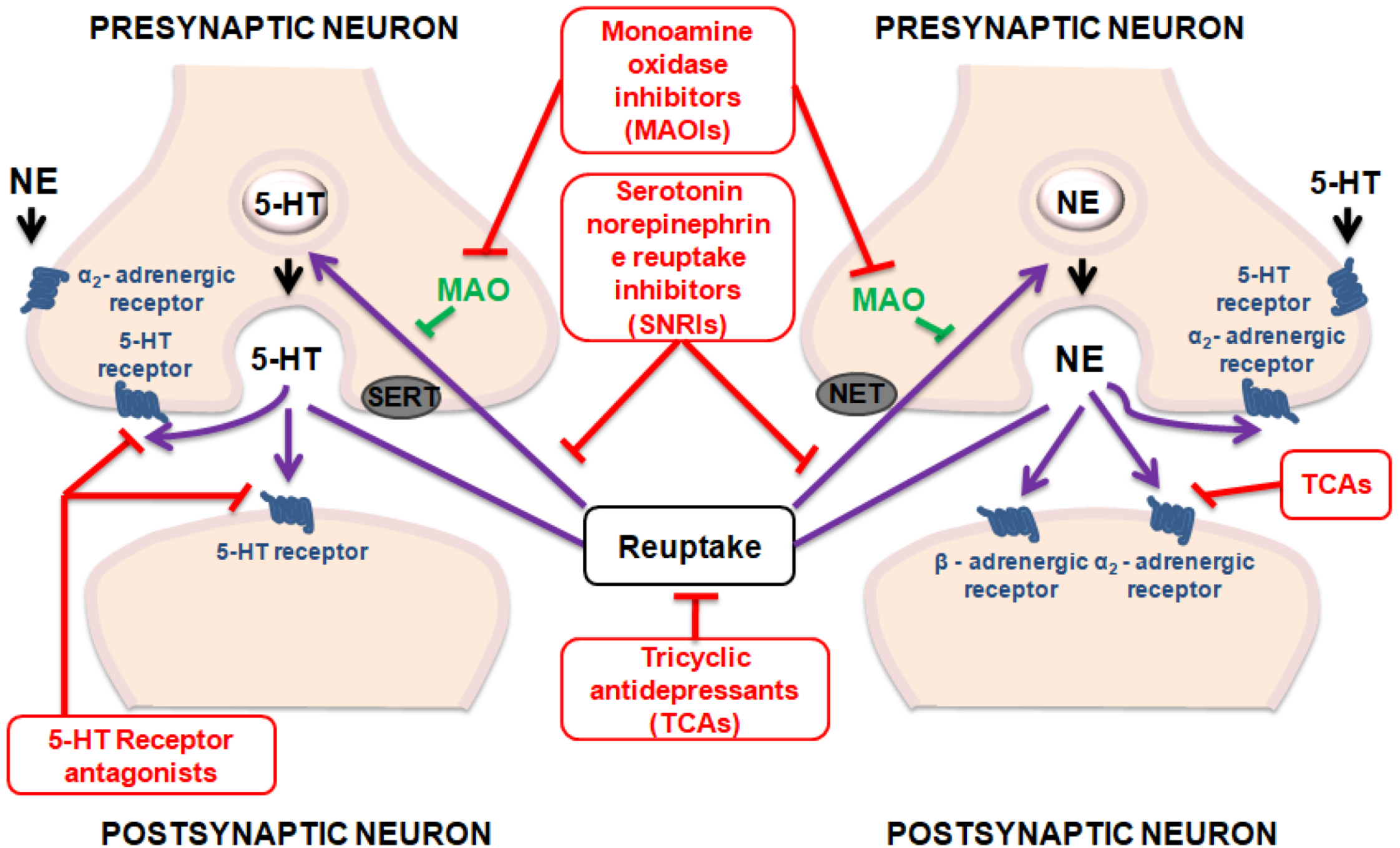




# Antidepressants – Different routes of action

- Neurotransmitters
  - Serotonin
  - Norepinephrine
  - Dopamine
- Reduction of neurotransmitter level  
→ imbalance → depression





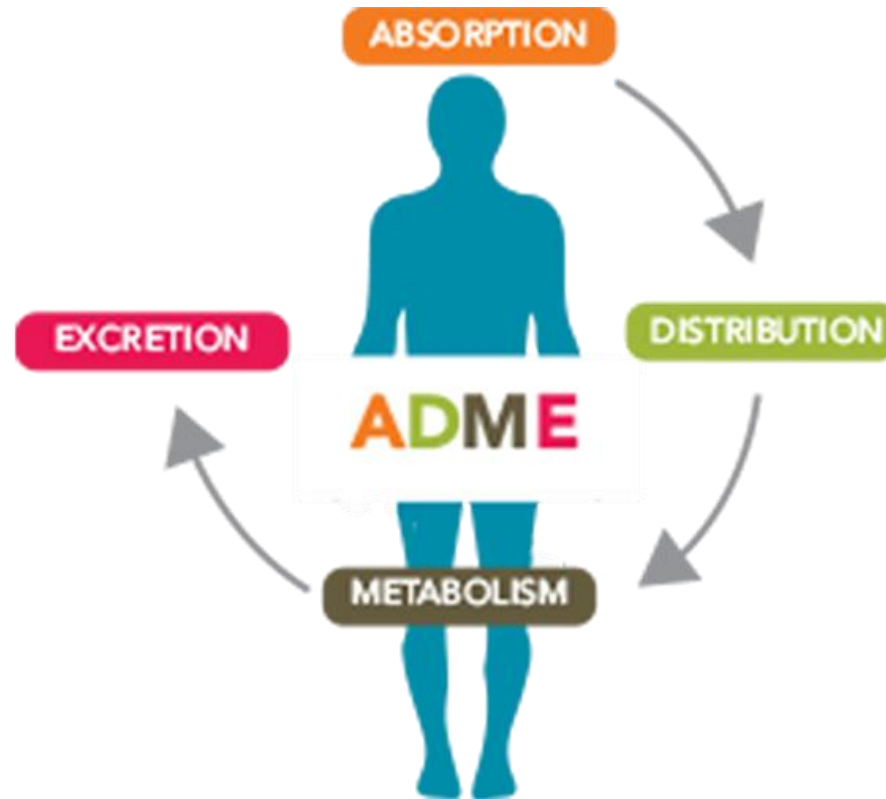
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**ADME**





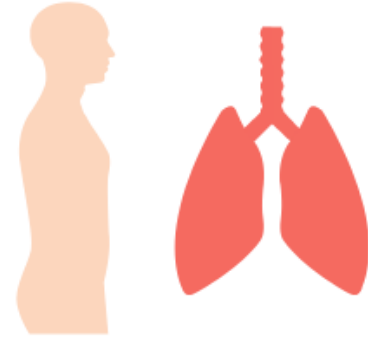
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# Drug administration routes



Oral route



Inhalation  
administration



Nasal  
administration

Rectal

Intramuscular

Subcutaneous



Intravenous  
route

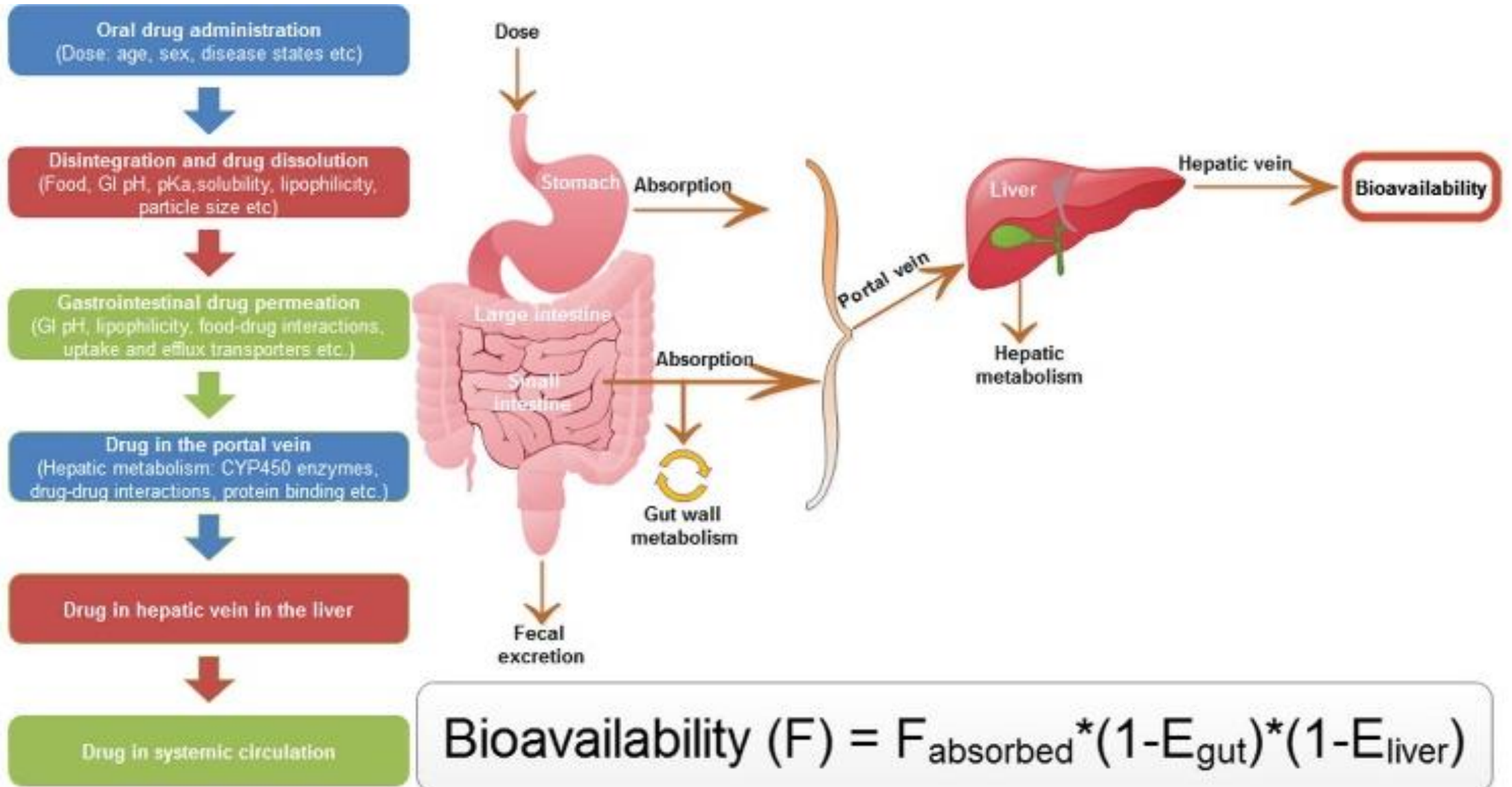


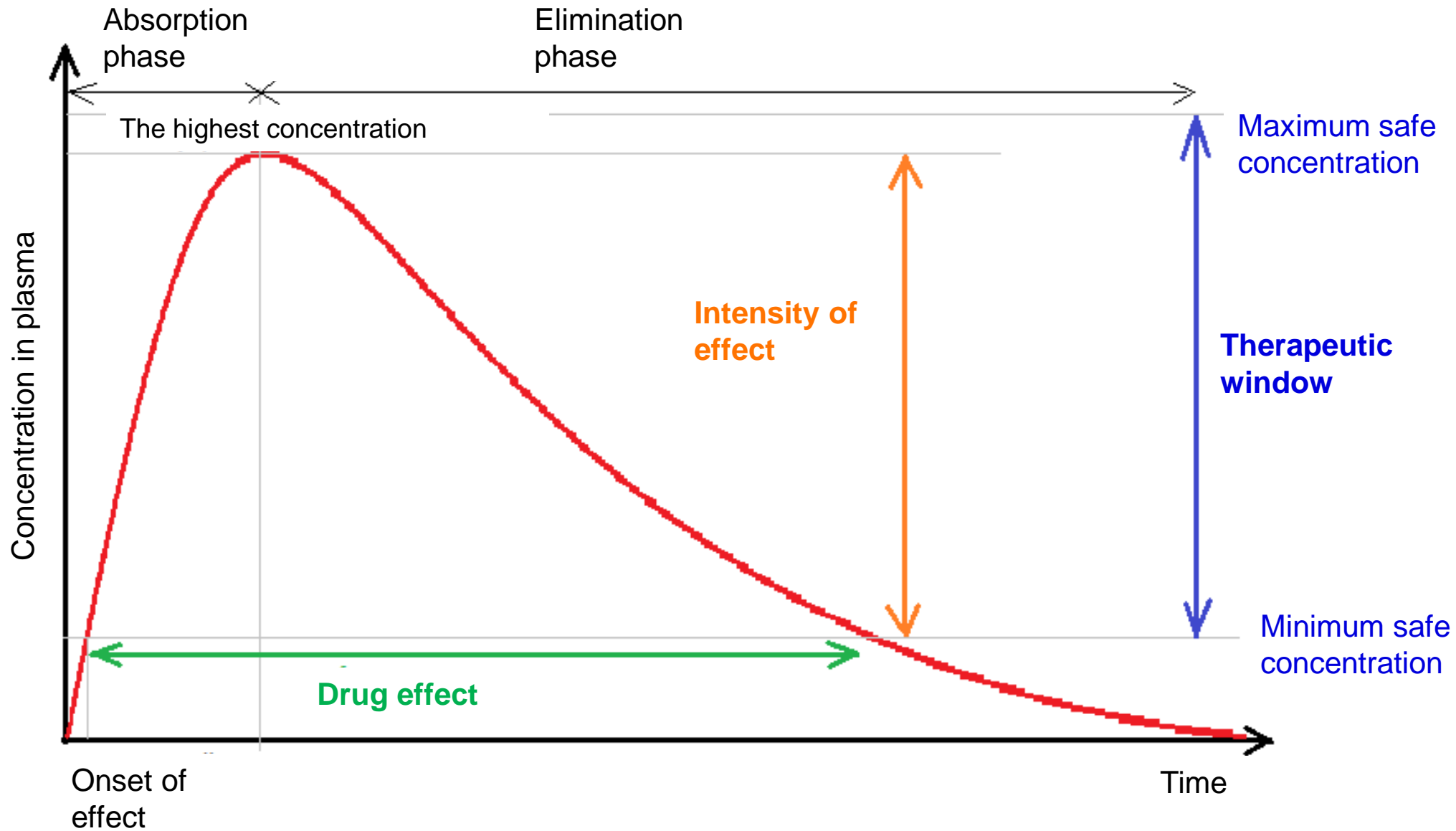
Ocular drug  
delivery



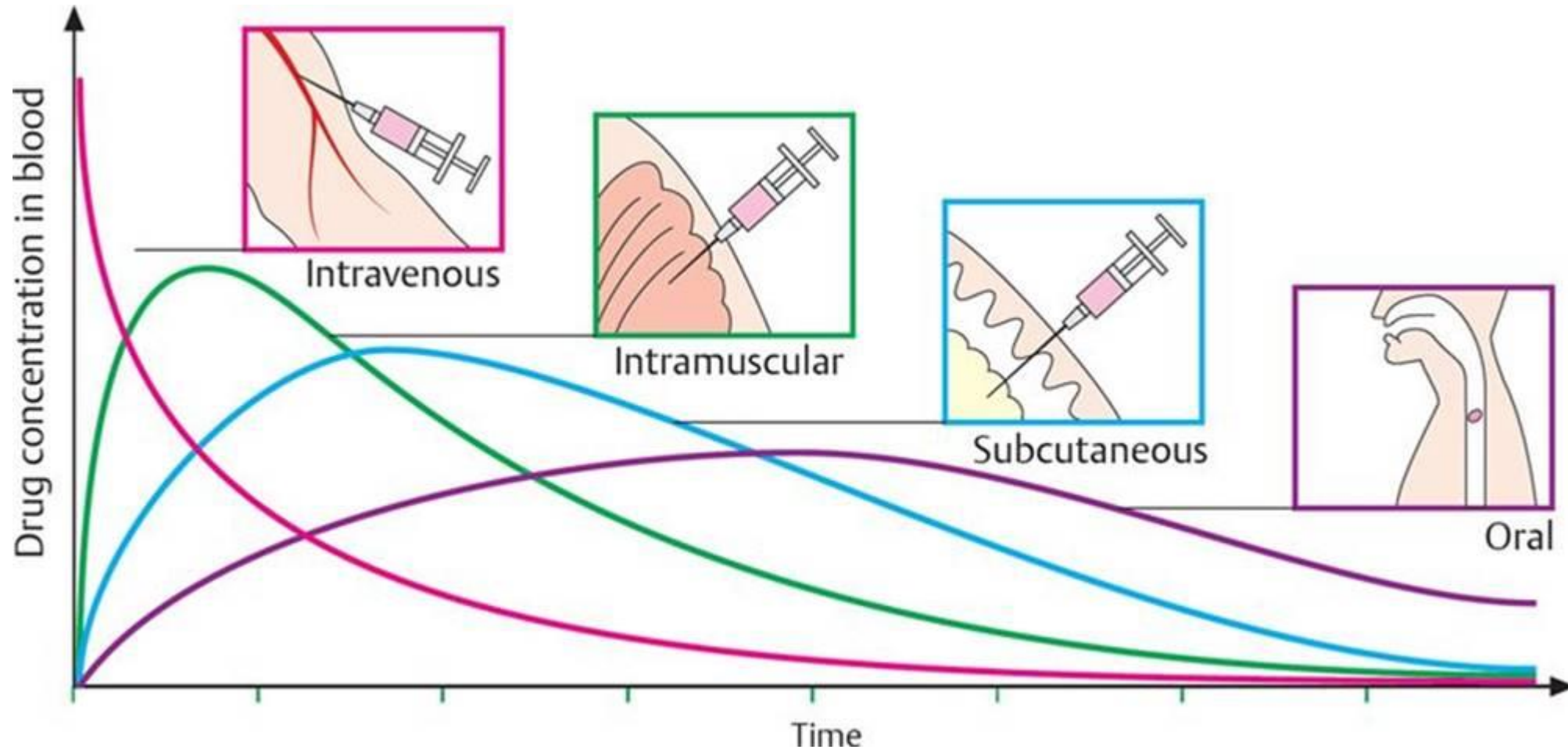
Transdermal  
diffusion

# Absorption, Distribution

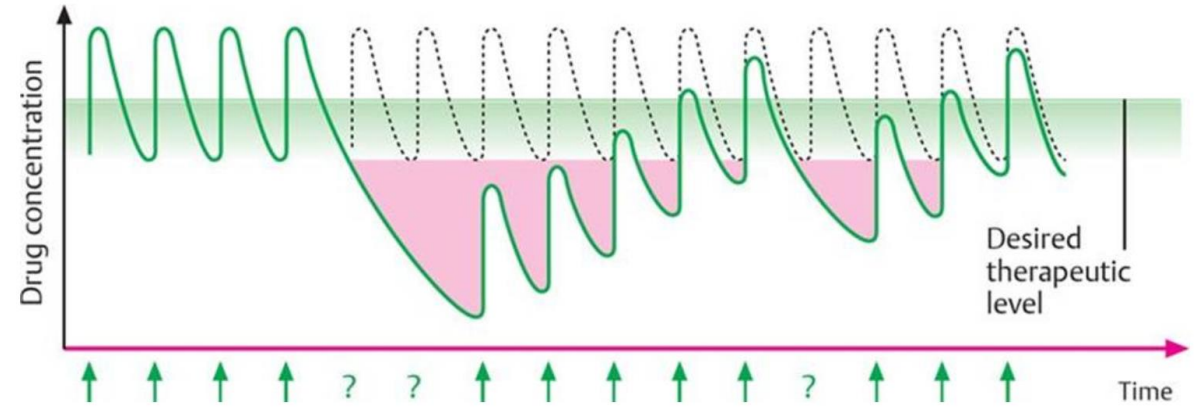
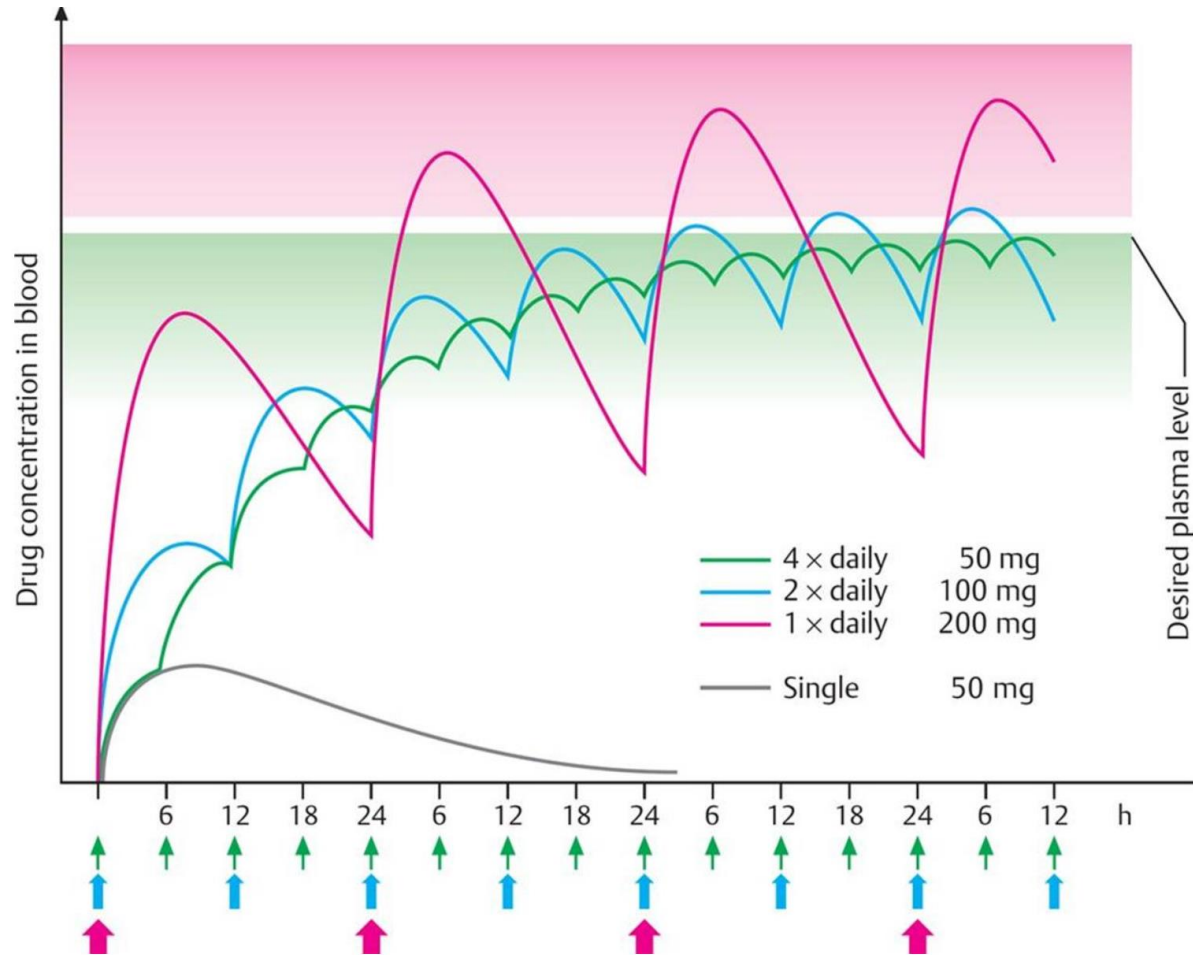








# Missing dose?



# Lipinski's rule

- Very good absorption/distribution
  - small molecule
  - moderately lipophilic

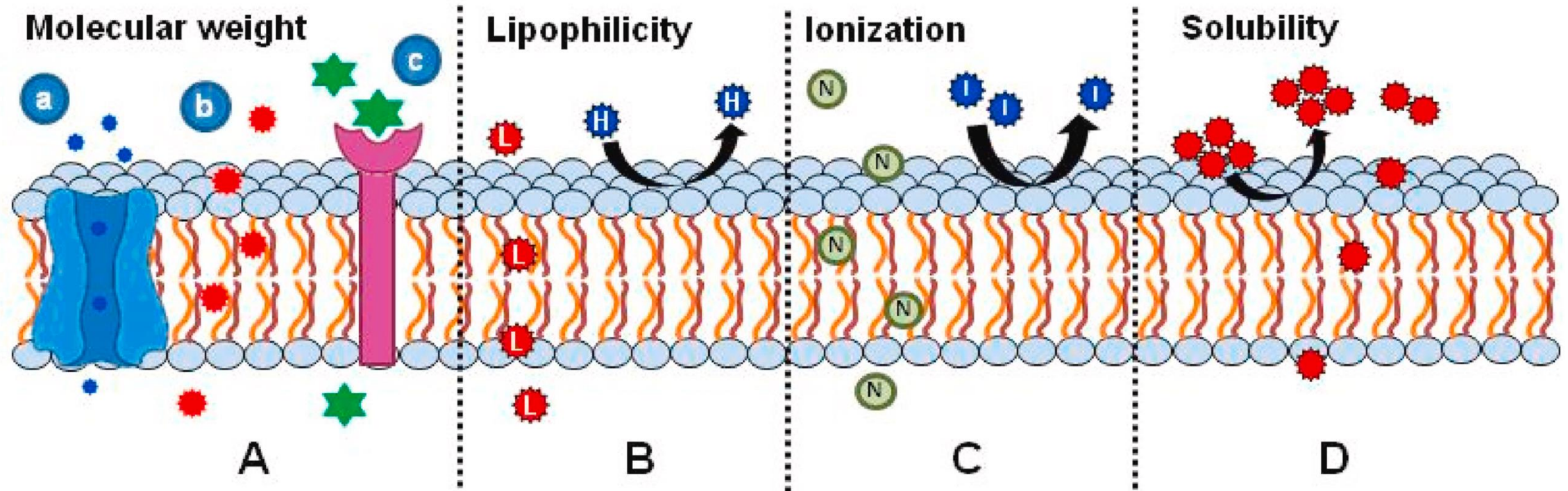
This famous "Lipinski's rule" has been highly influential in this regard, but only about 50 % of orally administered new chemical entities actually obey it.

# Lipinski's rule

- No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds)
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- A calculated octanol-water partition coefficient (Clog  $P$ ) that does not exceed 5



# Lipinski's rule

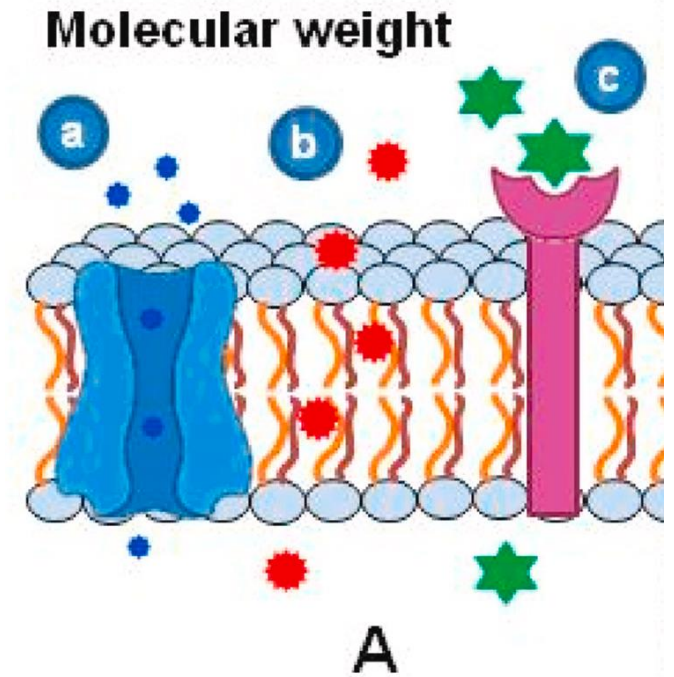


# Lipinski's rule

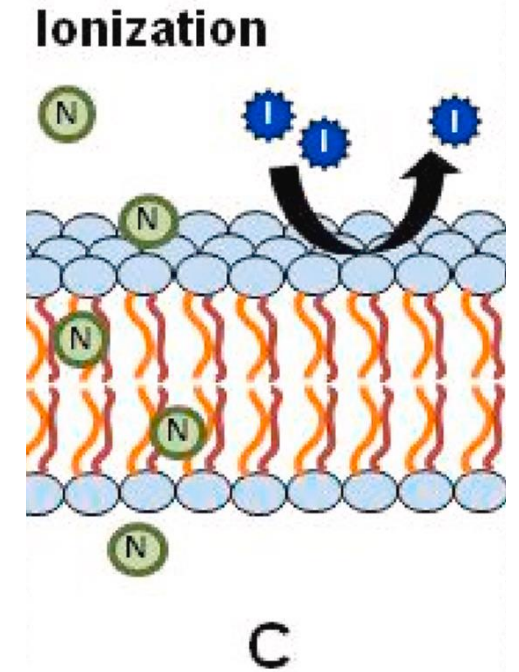
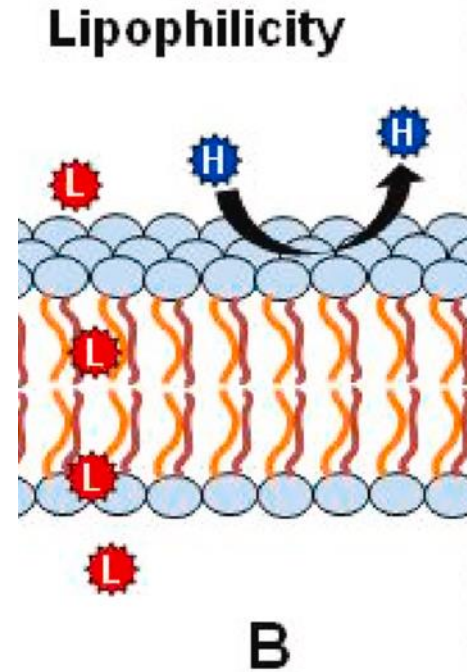
+ Very low molecular weight polar molecules

+ Low to medium molecular weight non-polar molecules

- High molecular weight molecules



# Lipinski's rule



Lipophilic

and non-ionic molecules

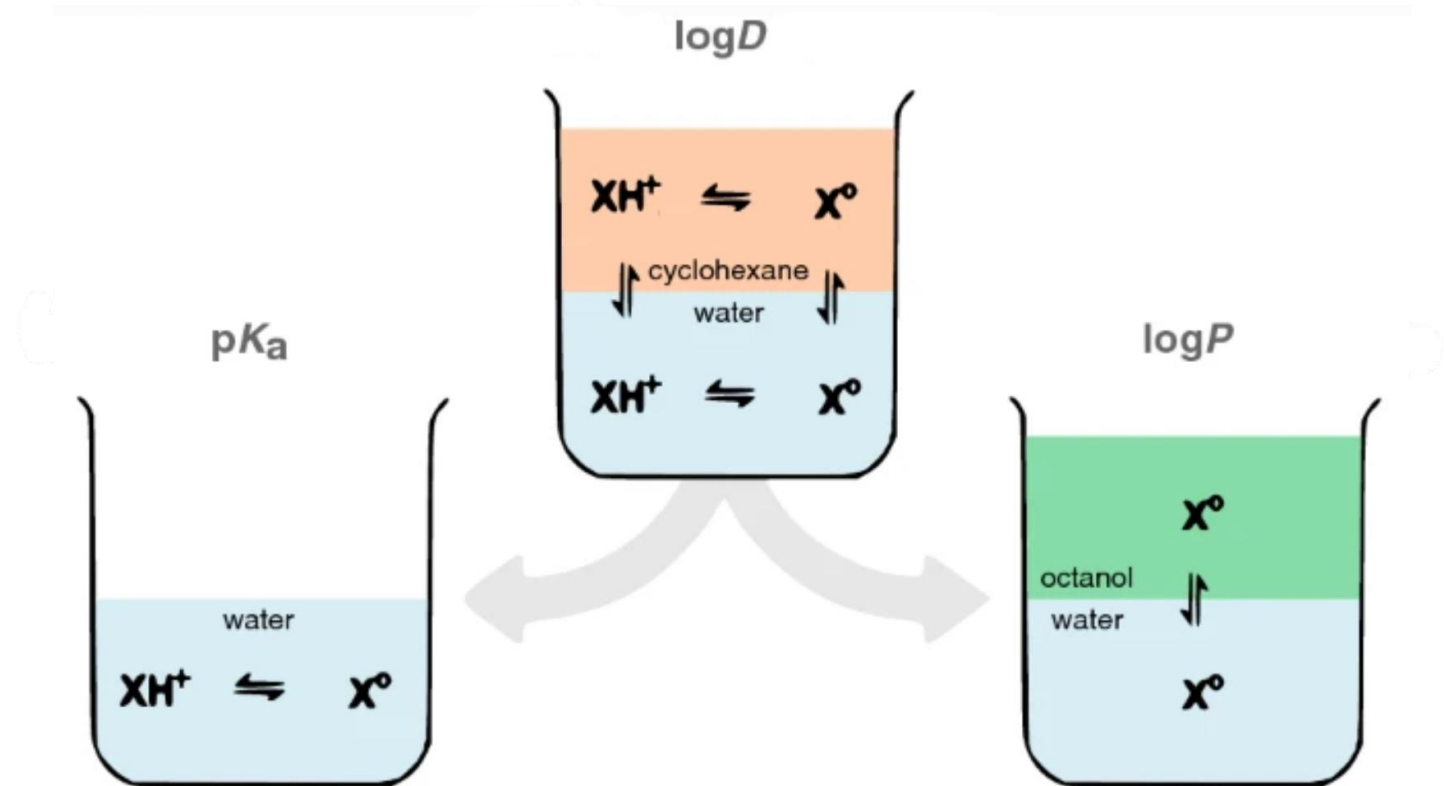
# Hydrophilic vs Lipophilic

- Affinity for water
  - HYDROPHILIC -water loving
  - LIPOPHOBIC -lipid hating
  
- Affinity for oil
  - LIPOPHILIC - lipid loving
  - HYDROPHOBIC- water hating

Partition coefficient

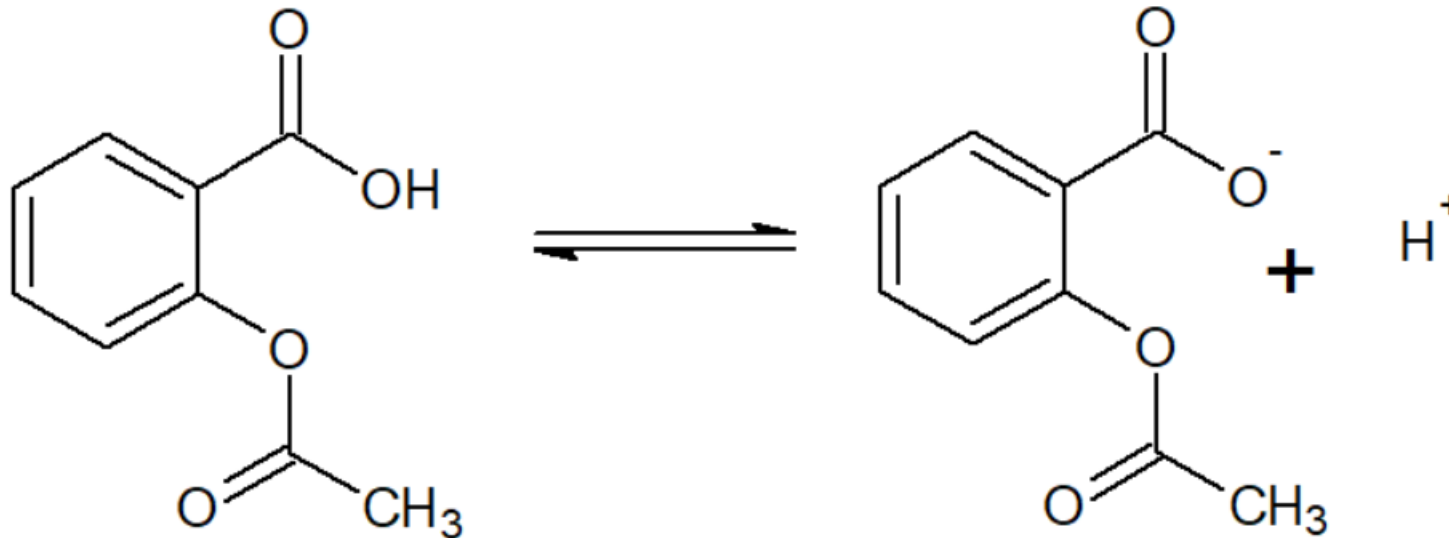
Distribution coefficient

$$\left. \begin{array}{l} \text{Partition coefficient} \\ \text{Distribution coefficient} \end{array} \right\} \text{Log } D = \frac{[X]_{\text{oil}}}{[X]_{\text{water}}}$$





# Ionization



acetylsalicylic acid is undissociated in the stomach

NON-Ionized form

acetylsalicylic acid is dissociated in the small intestine and blood plasma

Ionized form

# Ionization

NON-ionized form

Ionized form

Organic phase



Water phase

NON-ionized form

Ionized form

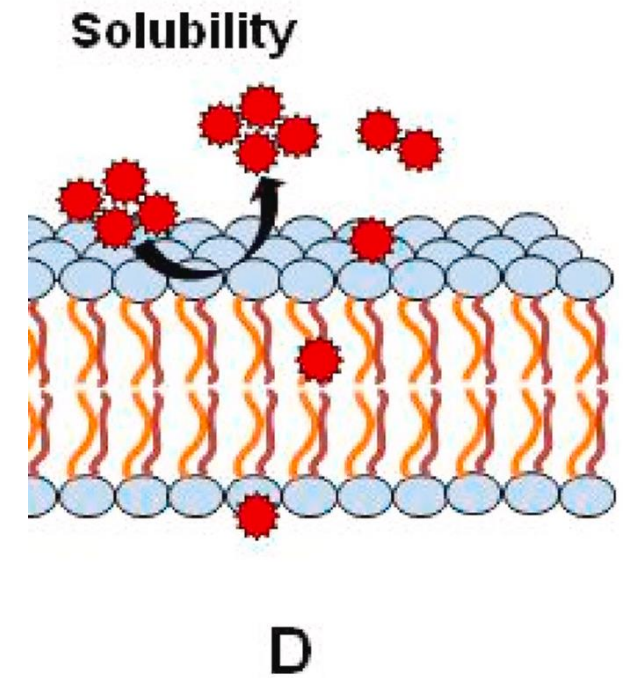


# Ionization

- Ionized form of the drug (charged, salt) dissolves in water and does NOT pass through the lipid membrane.
- NON-ionized form of the drug (free acid or base) dissolves in organic solvents and passes through the lipid membrane.

# Lipinski's rule

Only solubilized molecules can be absorbed





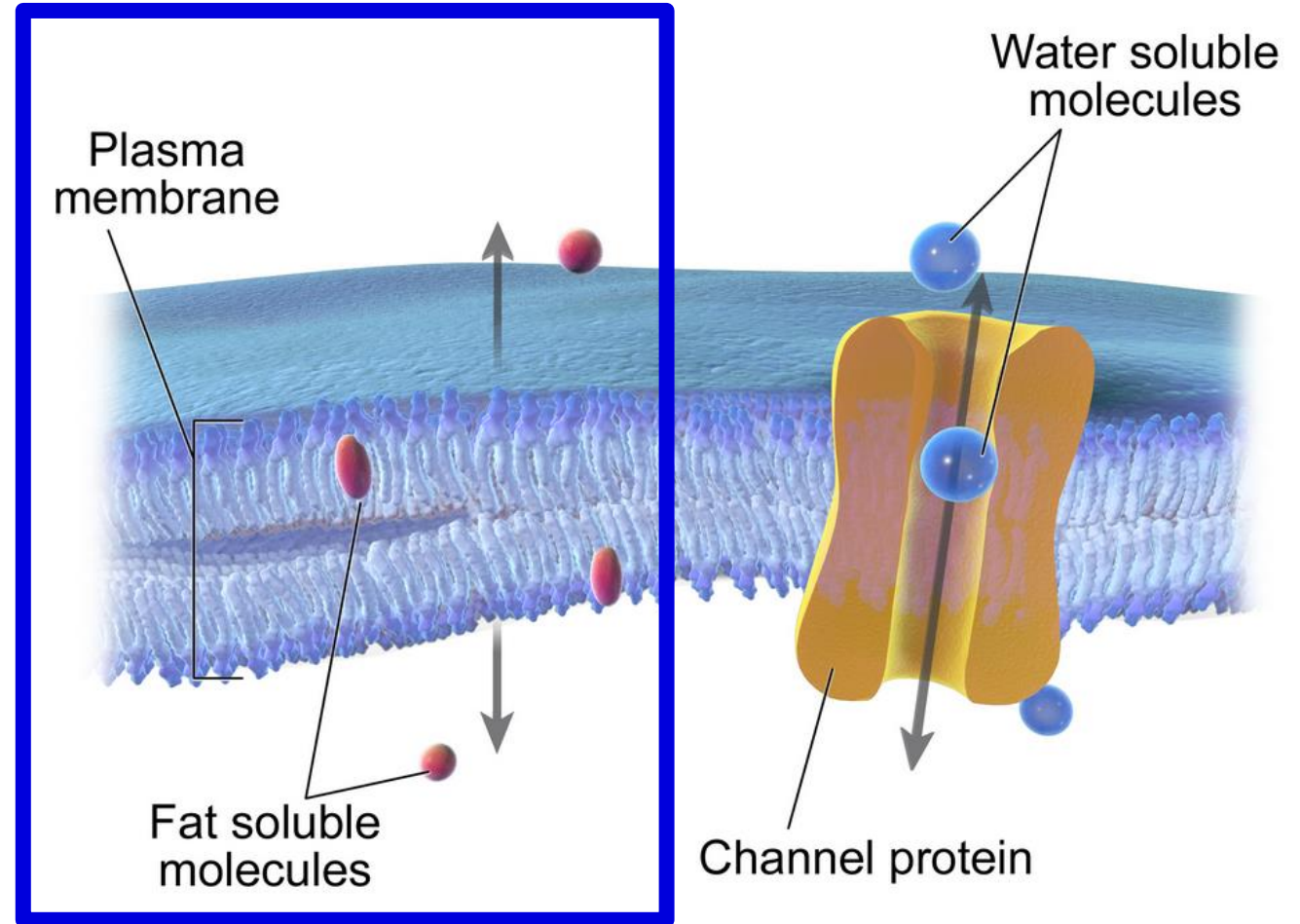
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# Distribution



# Passive diffusion

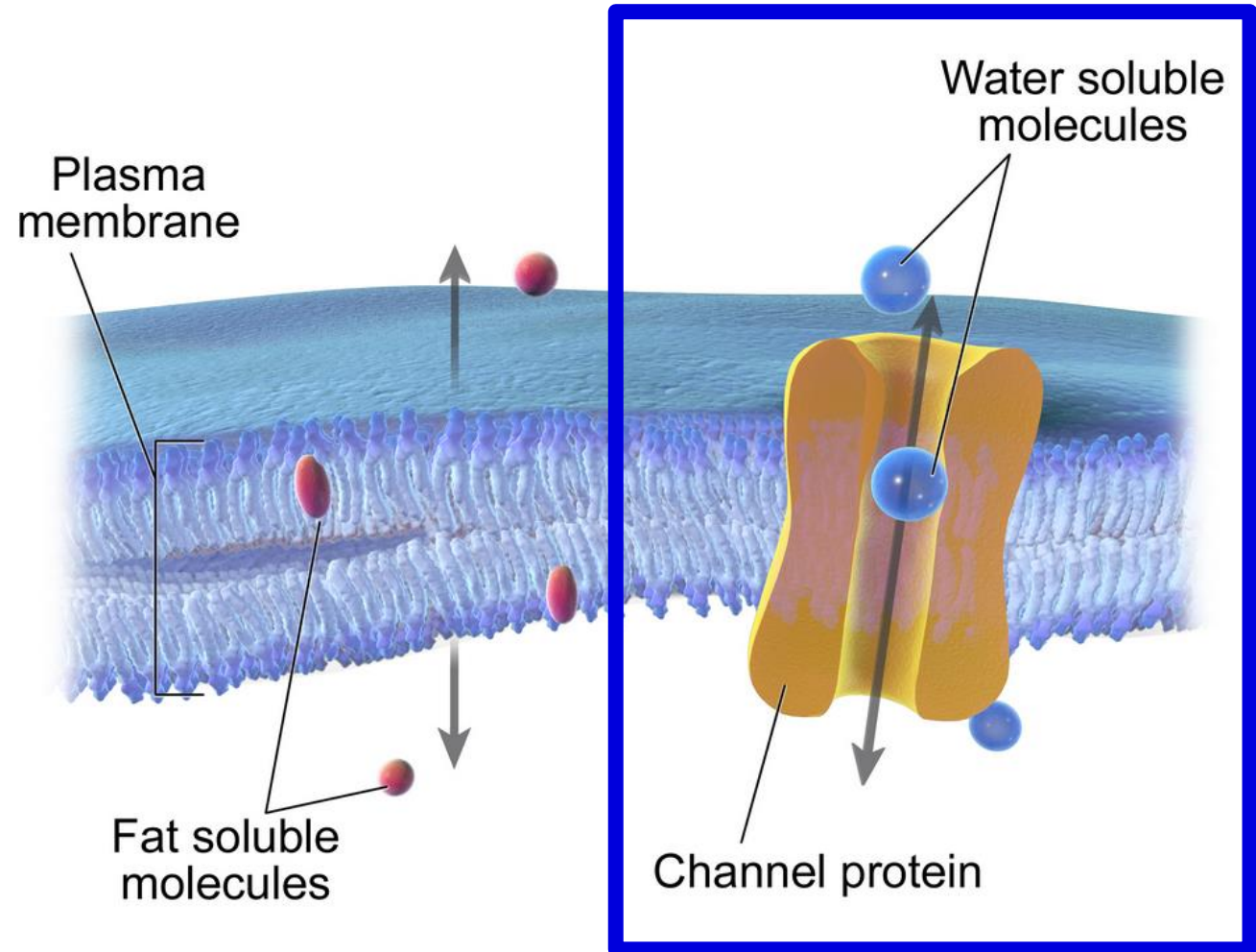
- Crossing of a substance across a cell membrane from an area of high drug concentration to an area of low drug concentration
- Passive process - that does not require energy
- Influencing factors:
  - lipid solubility
  - molecular size
  - degree of ionization



[https://en.wikipedia.org/wiki/Passive\\_transport](https://en.wikipedia.org/wiki/Passive_transport)

# Active Transport

- Needs help
- Requires energy
- Often a similar structure with endogenous substances such as ions, vitamins, sugars and amino acids.



[https://en.wikipedia.org/wiki/Passive\\_transport](https://en.wikipedia.org/wiki/Passive_transport)



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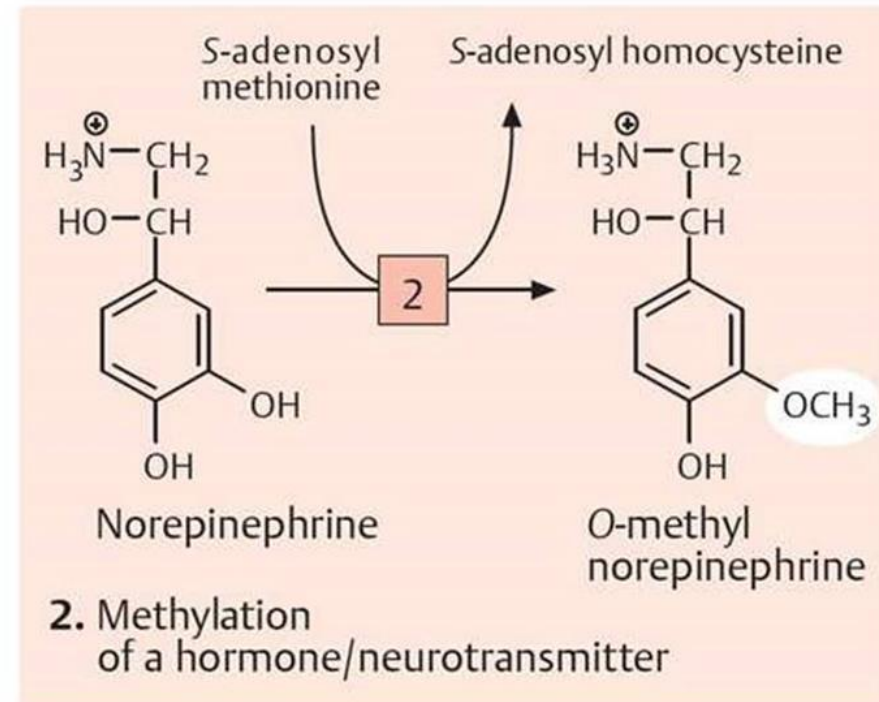
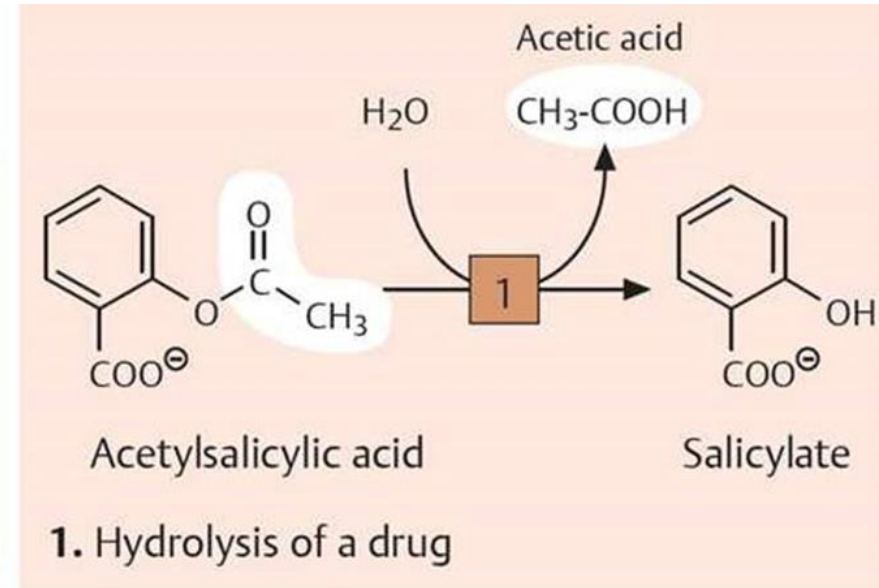
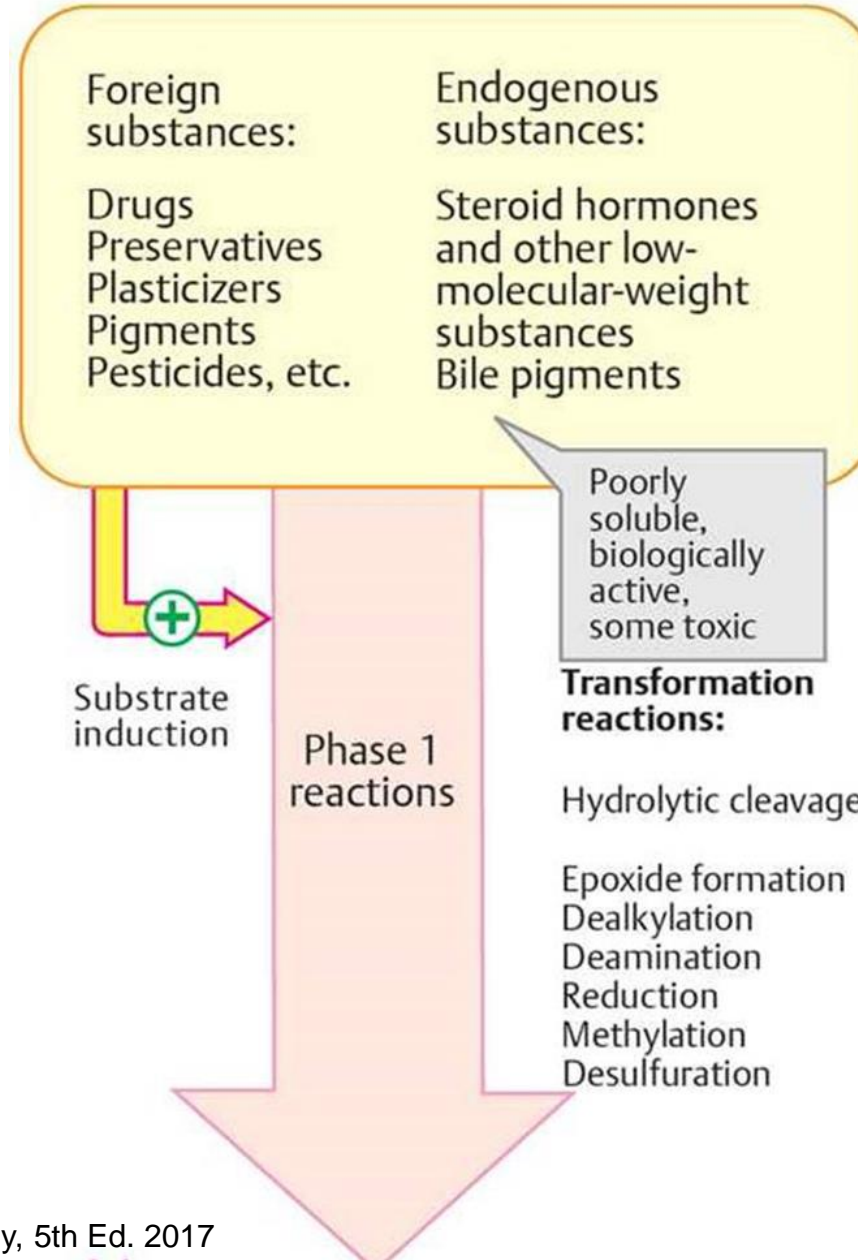
# Biotransformation/ Elimination



# Biotransformation - Liver

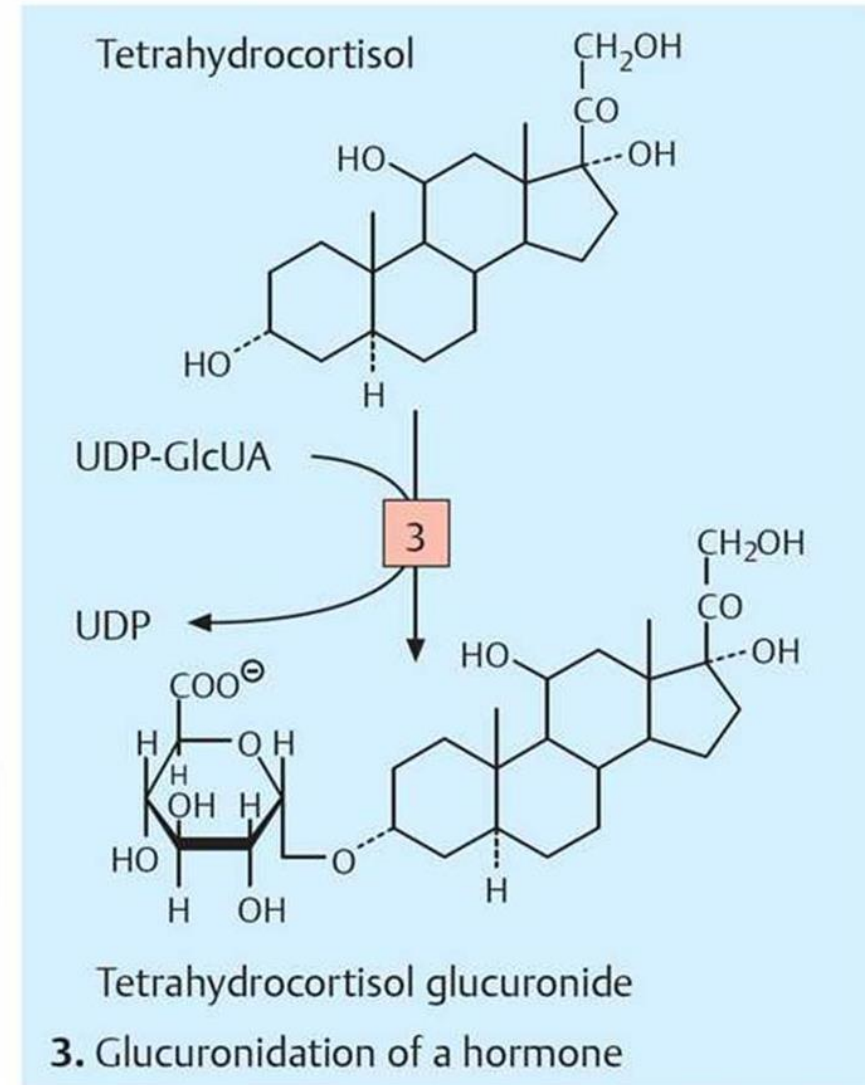
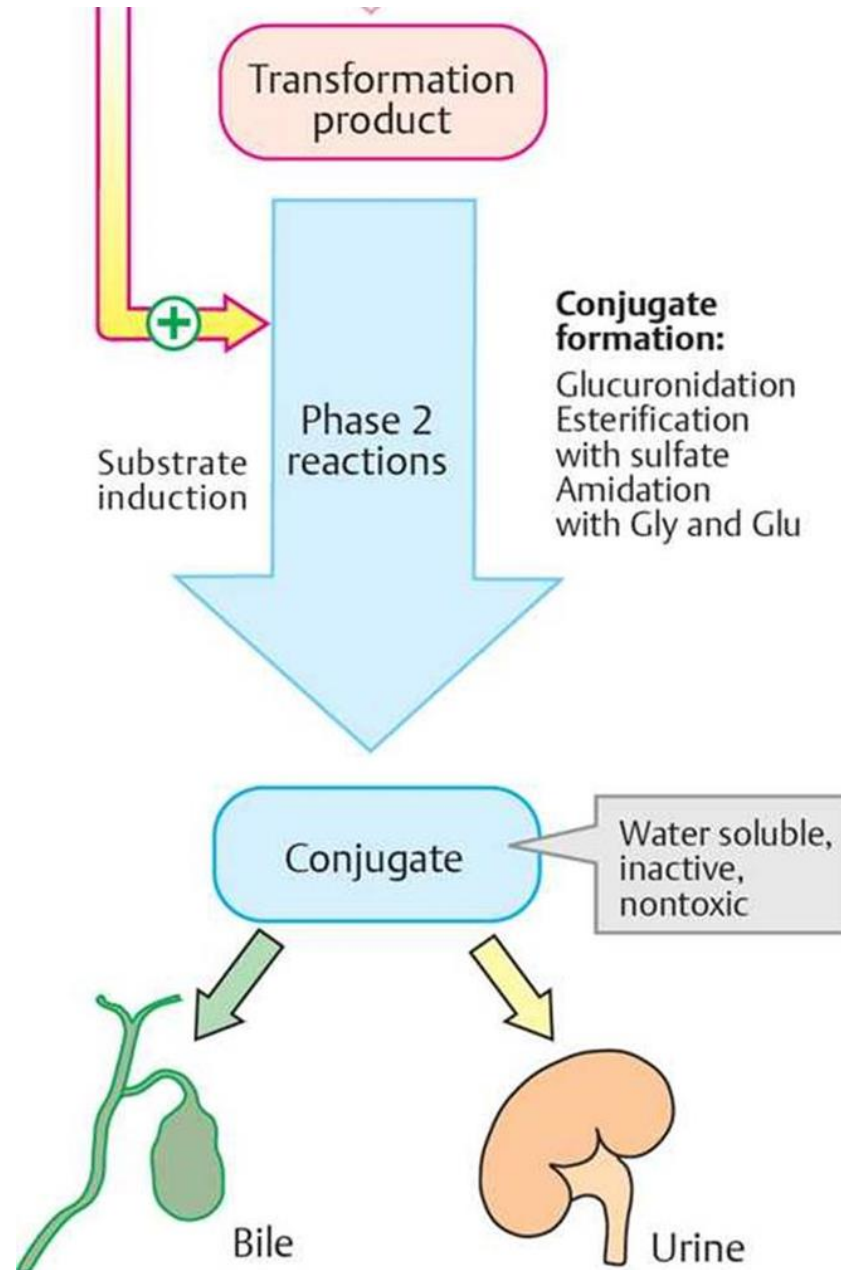
- Bank of various Superfamilies of enzymes
- **Cytochromoxidases (CYP)**
- **CYP450**
- Hydroxylases
- Reductases
- Glukuronyltransferases
- Oxidases

# Phase 1





# Phase 2



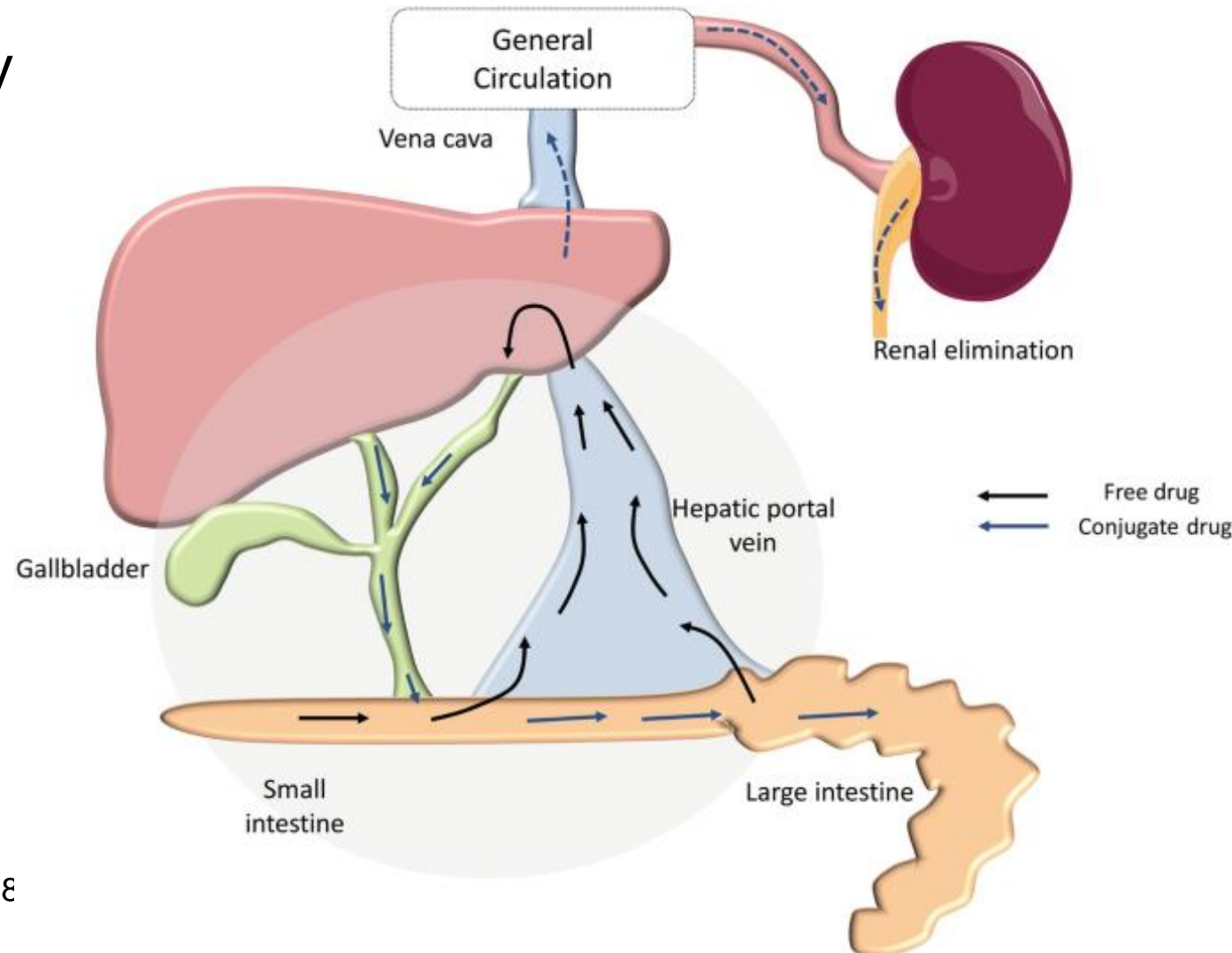
- 1 Arylesterase
- 2 Catechol-O-methyltransferase
- 3 Glucuronosyltransferase

# Elimination

- Bank of various Superfamilies of enzymes
- **Cytochromoxidases (CYP)**
- **CYP450**
- Hydroxylases
- Reductases
- Glukuronyltransferases
- Oxidases

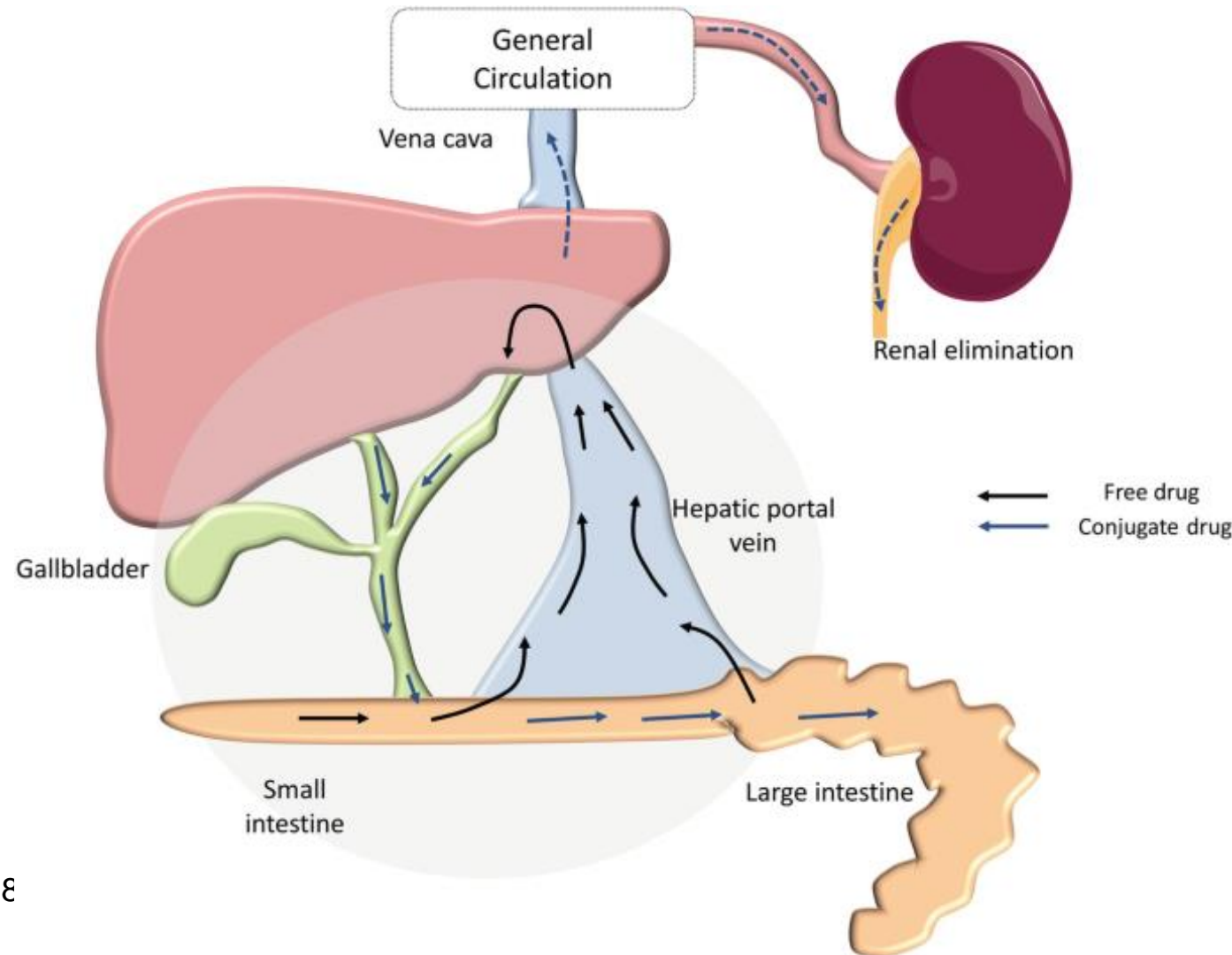
# Renal elimination - Kidney

- Drug must be filtered or actively transported into the urine
- Drugs are filtered into the urine from plasma depending on:
  - molecular weight
  - ionization
  - degree of protein binding



# Hepatic elimination

- Conjugated drugs - actively secreted into bile
- Unconjugated drugs → bacterial enzyme hydrolysis → reabsorption into the portal circulation





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**Is the design of  
medicines  
important?**



# Contents of a Tablet

- Excipients - inert compounds that can also serve as drug delivery systems.
- The composition of tablets - drug product remain stable
- Choosing the right packaging for the tablet is also important for its stability.
- Once the API (An active *pharmaceutical* ingredient) and excipients are perfected in a [medicinal chemistry](#) program, the next step in drug development is to decide on a suitable design for the tablet.



# Why Not Just Use a Plain White Tablet?

- Association of a drug's form with its function

- **MARKETING**

- **Viagra**



# Size Matters

- From tiny spheres to large, bulky rods.
  - Contain
  - target patient demographic
- difficulty swallowing larger pills
- tiny pills are harder to handle
- how small a pill can get is dependent on the dosage.

# Shape of Pills

- Shape can affect the dissolution of the drug
- Functional, easy to swallow

## COMMON TABLET SHAPES



ROUND



SQUARE



RECTANGLE



CAPSULE



ALMOND



PENTAGON



OVAL



LOZENGE



DIAMOND



TRIANGLE



CORE ROD



HEART

# Psychological Effects of Color

- Components of pills make them naturally white.
- The light blue color of Viagra - color of the sky → feelings of happiness and relaxation.



- Heart medications are colored red or pink → power and danger



# Psychological Effects of Color

- Components of pills make them naturally white.
- The light blue color of Viagra - color of the sky → feelings of happiness and relaxation.
- Heart medications are colored red or pink → power and danger
- No black tablets → death and other negative emotions.
- Greenish-yellow → sickness and disgust.
- The color of a tablet can influence patient compliance if they find it to be visually appealing.

# Colour – distinguishing different dosage

Coumadin (warfarin tablets)



Warfarin tablets (Barr brand)





# Additional Markings

- Certain words, numbers, or even symbols on the surface of tablet.
- Scored along the middle.
- more difficult for counterfeit versions of the drug to be manufactured.
- Special film coating or a unique flavor etc.

# Packaging

- Dose dispensing devices
- Applicators
- Combination of different drugs in one tablet – synergy effect
- Calendar packaging
- Wing top and screw cap openings, push-through blisters and suppositories with a slide system are favoured.

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