LECTURE OUTLINE
Introduction to Medicinal Chemistry - Lecture 15 & 16 Reading – Palleros (online)
- Drug Design: Pharmaceutical, Pharmacokinetic, and Pharmacodynamic Phases
HW set posted online

Medicinal Chemistry

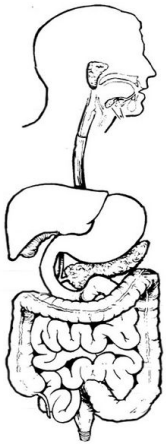
Pharmaceuticals → substance given to alleviate symptoms or treat the cause of a disease

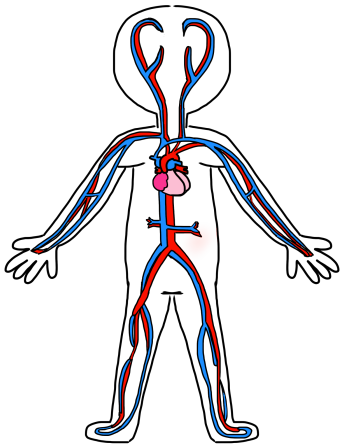
Potential vs. Effectiveness of a Drug Target

Administration:

Enteral
(oral/rectal)

Parenteral
(IV, intramuscular, subcutaneous, sublingual, topical, inhalation)





Barriers to drug effectiveness of a drug are broken down into 3 phases:

1. Pharmaceutical Phase

2. Pharmacokinetic Phase

3. Pharmacodynamic Phase

Pharmaceutical Phase: Administration to Absorption

Dosage form: tablet, solution, vapor

- In addition to the drug, dose may also include…

Potential for enzymatic degradation – what happens where?

Saliva

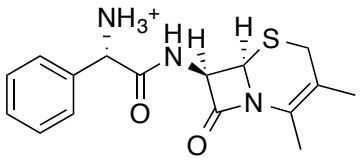
Stomach

Intestines

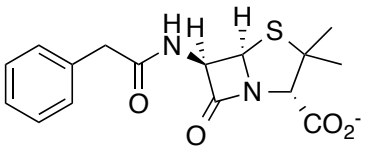
Pharmacokinetic Phase: Absorption, Distribution, Metabolism, Elimination (ADME)

Absorption into bloodstream requires drug to cross cell-membrane(s)

Structures of two antibiotics at physiological pH – what conditions would each be absorbed?



Cephalexin
(a cephalosporin)

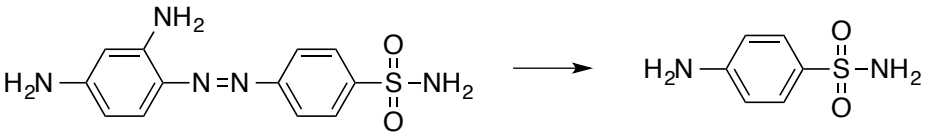


Penicillin G

Blood-brain barrier

Distribution into circulatory system

Metabolism – will it make it to its target receptor intact?



Prontosil
inactive prodrug

Sulfanilamide
active

HYDROLYSIS = easiest metabolic process to predict (look for carboxylic acid derivatives)

Excretion

Half-life

Pharmacodynamic Phase: drug interacts with receptor, elicits effects

Specific Drug-Receptor Interactions

Covalent Binding vs. Intermolecular Forces

Therapeutic Index, TI = LD_{50} / ED_{50}

Lethal Dose, LD_{50} - concentration at which 50% of test subject die

Effective Dose, ED_{50} – dose at which 50% of patients get desired effect

Biophores – screening of 10s-1000s of potential targets ("hits")

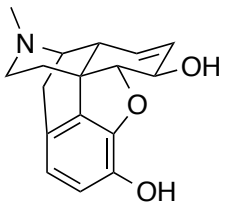
Pharmacophore

Toxicophore

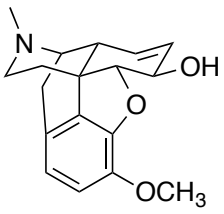
Metabophore

Auxophore

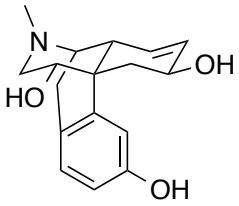
Identification of Pharmacophore through "derivatization of a lead"
Opioid alkaloids:



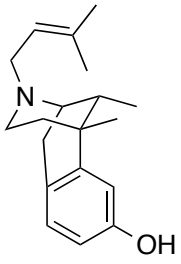
Morphine



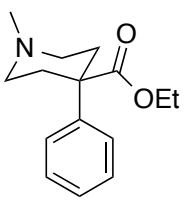
Codeine



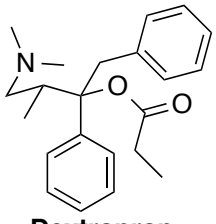
Levorphanol



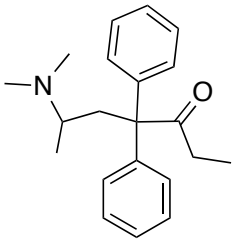
Pentazocine



Meperidine



Dextroprop-oxyphene



Methodone