INTRODUCTION TO PHARMACOLOGY: DRUG RECEPTORS AND PHARMACODYNAMICS.

Lecture 1
Pharmacology

• The study of substances that interact with living systems through chemical processes, especially binding to regulatory molecules and activating or inhibiting normal body processes.

• Medical pharmacology:
  • The science of substances used to prevent, diagnose and treat disease

• Toxicology
  • Branch of pharmacology that deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems.
Pharmacology

• 2 Major Divisions of Pharmacology

• Pharmacokinetics
  • Absorption, distribution and elimination of drug
  • Body to drug = how best to administer a drug

• Pharmacodynamics
  • Actions of the chemical on the organism
  • Drug to body = what is the drug of choice for a certain disease or condition

• The concept of the *drug receptor*
  • how a drug can affect the cell or organism
Pharmacology

- Pharmacogenomics
  - The study of the genetic variations that cause differences in drug response among individuals or populations

- What are drugs?
  - Any substance that brings about a change in biological function through its chemical actions
  - Usually of 2 types
    - Agonists = activator
    - Antagonists = inhibitor
  - Target molecule = receptors
    - Receptors are components of a cell or organism that interact with a drug and initiates the chain of events leading to the drug’s observed effects
Drugs

• 2 important concepts:
  1. ALL substances can, under certain circumstances, be toxic. (ex. the chemicals in botanicals/herbal medicines are no different from chemicals in manufactured drugs)
  2. ALL dietary supplements and all therapies promoted as health-enhancing, should meet the same standards of efficacy and safety as conventional drugs and medical therapies.

• Poisons = drugs that have almost exclusively harmful effects ("the dose makes the poison")
• Toxins = poisons of biological origin (synthesized by plants or animals)
Drugs

• A practical or useful drug must:
  1. must have the appropriate size, electrical charge, shape and atomic composition to interact with its target receptor
  2. Able to be transported from its site of administration to its site of action.
  3. Must be inactivated or excreted from the body at a reasonable rate, so that its actions will be of appropriate duration.
Drug Characteristics

- Physical nature of drugs
  - Solid, liquid or gas → can determine the best route of administration
  - May contain organic or inorganic elements
  - pH = may be acidic or basic (may alter absorption or excretion)

- Drug Size
  - Most drugs have a molecular weight between 100-1000
  - Significance
    - to have a good “fit” to only 1 type of receptor, a drug molecule must be sufficiently unique in shape, charge, etc., to prevent binding to other receptors
    - Must be able to move from one body compartment to another, and to stay within the affected compartment or area
Drug Characteristics

• Drug Shape
  • The shape must allow the drug to bind with its intended receptor

• Target receptors
  • May exist as activating and/or inhibiting receptors (may exist both at the same time)
  • 2 Main characteristics of receptors
    • Must be selective to a certain molecule or drug
    • Must change its function upon binding, in such a way that the function of the biologic system (cell, tissue, organ, etc) is altered
Pharmacodynamics

• Types of Drug-Receptor Interactions
  • Agonists = activate a receptor
  • Antagonists = binds to a receptor and competes with and prevents binding by other molecules → decrease effect of agonists
    • Reversible antagonist
      • increasing the amount of agonist can overcome the effect of the antagonist
    • Irreversible antagonist
      • No increase of agonist will overcome the antagonist
      • Irreversibly bound to the receptor
  • Allosteric chemicals
    • Will bind to the receptor molecule (not to the active site) to either further activate or further inhibit the action of a drug.
    • Not affected by concentration of agonist.
Pharmacodynamics

• Agonists
  • Full agonists = produces a full effect
  • Partial agonists = produces a less than maximal effect, no matter the concentration of the drug
    • Will bind to the target receptor and other non functional receptors = less response
  • Inverse agonist = prefers to bind to the inhibitory receptor than the activating receptor. = less than usual response.

• “Mimetic” drugs
  • These “mimic” agonist activity by inhibiting inhibitors
  • Ex. Ach → acetylcholinesterase → and Ach-ase inhibitors
Pharmacodynamics

- Duration of drug action may be determined by type of bonding of drug to the receptor
  - Effect will last as long as the drug is occupying the receptor
    - Drug dissociates from the receptor
    - Drugs that covalently bond to the receptor → receptor will eventually be destroyed by the cell and a new “empty” receptor will be produced
  - Drug effect may persist even after drug has left the receptor
    - Coupling molecules are still present (ex. 2nd messenger system effect)
    - Cells may incorporate a desensitization mechanism (ex. down regulation of receptors)
Pharmacodynamics

• **Drug binding**
  - Binds to a receptor = active binding site
  - Inert binding site
    - Binding of a drug to a non-regulatory molecule (ex. plasma albumin)
    - No detectable change in the function of the biologic system
    - Important when computing the correct dose of a drug.
Pharmacokinetics

• A good drug must have 4 characteristics
  1. Be **absorbed** by the body to the blood stream
  2. Be **distributed** to its intended site of action
  3. **Permeate** through the various barriers that separate each compartment
  4. Be **eliminated** at a reasonable rate (by metabolic inactivation or excretion)

• Usually in the form of a prodrug
  • An inactive precursor chemical that allows the drug to be absorbed and distributed, until it is converted to its active form at the target site.
Pharmacokinetics

1. Drug Absorption and Permeation
   - Aqueous diffusion
   - Lipid diffusion = most important limiting factor due to the numerous lipid barriers
   - Special carriers = transport proteins
     - Active or passive transport
   - Endocytosis of very large drugs/chemicals

1. Factors that affect distribution
   - Drug’s pH
   - Ionic charge (water or lipid soluble)
   - Affinity to inert binding sites (ex. albumin)
Pharmacokinetics

3. A drug’s pH and excretion

- Acidic or basic drug = charged (+/-) = more water soluble
- Non-charged or ionized drug = neutral = more lipid soluble
- Cell membranes = allows easy diffusion of lipid soluble drugs
- Excretion via kidneys
  - Weak acids excreted faster in alkaline urine
  - Weak bases excreted faster in acidic urine
- Absorption in stomach vs intestines
  - Acidic drugs = better absorbed in stomach
  - Basic drugs = better absorbed in intestines
Summary

- Pharmacology
- Drug and drug receptors
- Pharmacodynamics
  - Mechanism of action
- Pharmacokinetics
  - Route of administration
  - Elimination or excretion
- Side effects/contraindications/precautions
- To determine the drug of choice
  - Dosage and interval
Drug Receptors

- Receptors largely determine the quantitative relations between dose or concentration of drug and pharmacologic effects
  - Receptor-drug affinity = determines concentration of drug needed
- Receptors are responsible for selectivity of drug action
- Receptors mediate the actions of pharmacologic agonists and antagonists

- Interaction between drug and receptor is called *coupling*
Drug concentrations

- $EC_{50}$ = the concentration of a drug that produces 50% of maximal effect
- $E_{\text{max}}$ = maximal response that can be produced by a drug
- $ED_{50}$ = median effective dose = dose at which 50% of the population will exhibit the specified effect
- $TD_{50}$ = median toxic dose = 50% of the population will experience the toxic effect of the drug
- $LD_{50}$ = median lethal dose = 50% of the population will die at this dose (TD may be = to LD, if the toxic effect is death)
- $K_d$ = dissociation constant = concentration of a free drug at which half maximal binding to receptors are observed
  - High $K_d$ = low receptor affinity of a drug
  - Low $K_d$ = high receptor affinity of a drug
Relation bet drug dose and response

- Affinity = how easily a drug binds to a receptor
- Potency = concentration or dose of a drug required to produce 50% of that drug’s maximal effect ($EC_{50}$)
  - Lower dose to achieve 50% of its activity = highly potent
- Efficacy = maximum effect of a drug

Drugs A, B, C, D = high affinity
Potency: B>A>C>D
Efficacy: A=C=D>B
Relation bet drug dose and response

• Generally, response is directly proportional to amount of drug administered
  • However, doses may be reached at which no further increase in response can be achieved → all of the receptors have been bound to a drug
  • There are instances when a maximal response is achieved without full or complete receptor binding = presence of “spare” receptors
  • Other times, when an antagnostic drug is combined with an agonist a maximal response is still achieved, with a greater dose of the agonist. Until there comes a time when a maximal response can no longer be achieved.
Presence of spare receptors

![Graph showing agonist effect and EC₅₀ values](image)

- **A**: EC₅₀ (A)
- **B**: EC₅₀ (B)
- **C**: EC₅₀ (C)
- **D**: EC₅₀ (D, E) = Kᵅ

**Agonist concentration (C) (log scale)**

**Agonist effect**
Relation bet drug dose and response

- The sensitivity of a cell or tissue to a particular concentration of a drug depends not only on the affinity of the receptor for binding the drug, but also on the degree of spareness
  - Degree of spareness = The total number of receptors present compared with the number actually needed to elicit a maximal biologic response

- Therapeutic index
  - Ratio of TD$_{50}$ to ED$_{50}$
  - Relates the dose of a drug required to produce a desirable effect to that which produces an undesirable effect
  - Narrow or wide margin of safety vs severity of disease being treated
Relation between agonists and antagonists

- Agonist = activates a receptor
  - Full agonist
  - Partial agonist = produces a lower response, at full receptor occupancy
    - Acts like an irreversible antagonist, but with mild agonist activity
Relation bet agonists and antagonists

• **Antagonist** = prevents agonist from activating a receptor
  • Inverse agonist = reduces receptor activity below basal levels
  • Reversible antagonist
    • Competitive antagonist = progressively inhibits the agonist response. High antagonist concentrations prevent response completely.
      • Conversely, sufficiently high agonist concentrations can surmount the effect of a given antagonist
      • Agonist response curve is shifted to the right
  • Irreversible antagonist
    • Also non-competitive antagonist
    • The receptor becomes unavailable for binding by the agonist (covalent bond)
    • Antagonists may bind directly on the binding site or to a different binding site of the receptor = either reversible or irreversible = conformational change to the receptor
Relation bet agonists and antagonists

• Other mechanisms of drug antagonism
  • Chemical antagonist
    • Does not rely on the drug receptor. Instead, the antagonist directly binds to the agonist making it inert or unable to bind with the receptor
  • Physiologic antagonist
    • Sympa vs parasympa drugs.
    • Steroids or glucagon vs insulin on blood glucose effect
Signaling mechanisms and drug action

• 5 basic mechanisms of transmembrane signaling (how a drug affects a receptor to produce a response)
  • Lipid soluble ligand
  • Transmembrane receptor protein that directly acts on a cell
  • Transmembrane protein that activates tyrosine kinase
  • Activates gated ion channels
  • Stimulates G-proteins and the 2nd messenger system
Other Responses to drugs

- Desensitization = after reaching an initial high level, the response diminishes over time, even in the continued presence of the agonist
  - Usually reversible
- Tolerance = responsiveness decreases over a continued presence of the drug
  - Tachyphylaxis = when responsiveness diminishes rapidly after administration
- Hypo or hyperreactive to the drug = increased or decreased response compared to the usual (usually genetic in nature)
- Hypersensitivity to the drug = allergy
- Idiosyncratic reactions = unknown reason/reaction
What causes variation in drug responsiveness?

- 4 general mechanisms
  1. Alteration in concentration of drug that reaches the receptor
  2. Variation in concentration of endogenous receptor ligand
  3. Alterations in number or function of receptors
  4. Changes in components of response distal to the receptor
What causes variation in drug responsiveness?

1. Alteration in concentration of drug that reaches the receptor
   - Patients may differ in the rate of absorption of a drug, in distributing it through body compartments or clearing the drug from the blood or body.
   - Age, sex, weight, disease state, liver and kidney function
   - Genetic differences (ex. inheritance of diseases that lack certain enzymes for drug metabolism)
What causes variation in drug responsiveness?

2. Variation in concentration of endogenous receptor ligand
   - Some disease states will increase receptor-ligand activity
     (pheochromocytoma will produce more catecholamines → thus propranolol will be more effective to this patient than to a normal healthy individual)
What causes variation in drug responsiveness?

3. Alterations in number or function of receptors

• Due to a change in number of receptors or to the efficiency of coupling
• Some disease states will produce more receptors (hyperthyroidism can increase β receptors in the heart = propranolol will be more effective in decreasing heart rate)
• Too much exposure to a drug can cause down or up regulation of receptors = produce “overshoot” phenomena during drug withdrawal
  • Too much antagonist = produce more receptors = once the drug is removed, there will be an exaggerated response
  • Similarly = too much agonist = decrease receptors = decrease effect of a drug
What causes variation in drug responsiveness?

4. Changes in components of response distal to the receptor
   • Patient characteristics that may alter or limit response to a drug
     • Age, general health, sex
     • More importantly = disease state
       • How severe or how mild the disease is can affect response to a drug
       • Is it the right diagnosis or are we missing anything? = always the right drug for the right patient.
Clinical selectivity: good vs bad

- No drug causes only a single, specific effect
  - Drugs may be selective, but never 100% specific to just 1 receptor
  - Binding to other receptors may cause some other effects
  - Toxic effects = side effect = adverse effect

- Therapeutic strategies
  1. The drug should always be administered at the lowest dose that produces acceptable benefit
  2. Adjunctive drugs (or combining drugs) may allow lowering the dose of the first drug, thus limiting its toxicity
  3. Manipulate the concentration of drug to the affected body part or compartment (ex. use inhaler instead of tablet; use topical instead of tablet)

- Choose a drug with a wide therapeutic index