Pharmacodynamics

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Introduction

- Pharmacology is the study of the biochemical and physiological aspects of the drug effects including absorption, distribution, metabolism, elimination, toxicity and specific mechanism of action.

- The main areas of pharmacology are:
  - **Pharmacokinetics**: the way the body handle drug absorption, distribution, biotransformation, and excretion.
  - **Pharmacodynamics**: the study of the biochemical and physiological effect of the drugs and their mechanism of action.
FIGURE 1-1 ▼ Areas of study within pharmacology.
Pharmacodynamics

- Drug targets are usually receptors or enzymes. The drug needs to bind a sufficient number of target protein at a reasonable dose, so the drug should be potent.

- The study of the biochemical and physiological effect of the drugs and their mechanism of action.

- The study of the relationship of drug concentration to drug effects.
Biochemical Classes of Drug Targets of Current Therapies

N = 483

- Receptors, 45%
- Enzymes, 28%
- DNA, 2%
- Hormones & factors, 11%
- Ion channels, 5%
- Nuclear receptors, 2%
- Unknown, 7%
Mechanism of drug action

- Most drugs exert their effect by interacting with a specialized target macromolecules, called receptors, present on the cell surface or intracellularly.

- The receptors will transduce the binding into a response by causing a conformational changes or biochemical effect.
Mechanism of drug action

- Receptors are large macromolecules with a well-defined 3D shape.

- The two fundamental properties underlying specificity in drug-receptor interactions are complementarity of shape between drug and receptor, and complementarity between the electrostatic, hydrophobic, and hydrogen bonding surfaces of each component.
Lock and key
Receptors

- determine specificity of drug action
- *most* are proteins
- Most drugs bind reversibly (noncovalent)
- not all “drugs” use receptors
Major receptor families

- Ligand-gated ion channels
- G protein-coupled receptors
- Enzyme-linked receptors
- Intercellular receptors
Ligand-gated ion channels

- Responsible for regulation of the flow of ions channels across cell membranes.

- Regulated by binding of a ligand to the channels.

- The best example being the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle.
G protein-coupled receptors

• Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins.

• Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors depend n the G proteins) mediate their action on cells.
Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme.

- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein.

- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch.
Figure 15-52. Molecular Biology of the Cell, 4th Edition.
C. Ligand-regulated enzyme

Insulin

 Tyrosine kinase

Phosphorylation of tyrosine-residues in proteins
**Intercellular receptors**

- In this family the ligand must diffuse into the cell to interact with the receptors.

- Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes.

- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression.
Protein synthesis-regulating receptor
HOW DO DRUGS WORK?

Most work by interacting with endogenous proteins:

- Some antagonize, block or inhibit endogenous proteins
- Some activate endogenous proteins
- A few have unconventional mechanisms of action
HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

• Antagonists of Cell Surface Receptors

• Antagonists of Nuclear Receptors

• Enzyme Inhibitors

• Ion Channel Blockers

• Transport Inhibitors

• Inhibitors of Signal Transduction Proteins
A receptor that is embedded in the cell membrane and functions to receive chemical information from the extracellular compartment and to transmit that information to the intracellular compartment.
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

KEY CONCEPTS:

• Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.

• Some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response.

• When cell surface receptors bind the molecule, the endogenous chemical cannot bind to the receptor and cannot trigger a response.

• The compound is said to “antagonize” or “block” the receptor and is referred to as a receptor antagonist.
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Extracellular Compartment

Unbound Endogenous Activator (Agonist) of Receptor

Cell Membrane

Inactive Cell Surface Receptor

Intracellular Compartment
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Extracellular Compartment

Bound Endogenous Activator (Agonist) of Receptor

Cell Membrane

Active Cell Surface Receptor

Intracellular Compartment

Cellular Response
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Extracellular Compartment

Cell Membrane

Intracellular Compartment

Displaced Endogenous Activator (Agonist) of Receptor

Bound Antagonist of Receptor (Drug)

Inactive Cell Surface Receptor Upon being Bound
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

- Displaced Endogenous Activator (Agonist) of Receptor
- Bound Antagonist of Receptor (Drug)
- Inactive Cell Surface Receptor Upon being Bound
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Footnote:

Most antagonists attach to binding site on receptor for endogenous agonist and sterically prevent endogenous agonist from binding.
If binding is reversible - Competitive antagonists
If binding is irreversible - Noncompetitive antagonists

However, antagonists may bind to remote site on receptor and cause allosteric effects that displace endogenous agonist or prevent endogenous agonist from activating receptor. (Noncompetitive antagonists)
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Cell Membrane

Extracellular Compartment

Displaced Endogenous Activator (Agonist) of Receptor

Bound Antagonist of Receptor

Active Receptor

Inactive Receptor

Allosteric Inhibitor

Intracellular Compartment
ARE DRUGS THAT ANTAGONIZE CELL SURFACE RECEPTORS CLINICALLY USEFUL?

Some important examples:

Angiotensin Receptor Blockers (ARBs) for high blood pressure, heart failure, chronic renal insufficiency (losartan [Cozaar®]; valsartan [Diovan®])

Beta-Adrenoceptor Blockers for angina, myocardial infarction, heart failure, high blood pressure, performance anxiety (propranolol [Inderal®]; atenolol [Tenormin®])
Drug Receptor Interactions

A. Agonist
   - A + Receptor → Positive Effect
   - A + C + Receptor → A+C + Effect

B. Competitive inhibitor
   - A + Receptor → A alone + Effect
   - A + B + Receptor → A+B + Effect
   - A + D + Receptor → A+D + Effect

C. Allosteric activator
   - A + Receptor → A+C + Effect
   - A + B + Receptor → A+B + Effect
   - A + D + Receptor → A+D + Effect

D. Allosteric inhibitor
   - A + Receptor → A alone + Effect
   - A + B + Receptor → A+B + Effect
   - A + D + Receptor → A+D + Effect

Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology,
HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors

- Enzyme Inhibitors

- Ion Channel Blockers

- Transport Inhibitors

- Inhibitors of Signal Transduction Proteins
ARE DRUGS THAT ANTAGONIZE NUCLEAR RECEPTORS CLINICALLY USEFUL?

Some important examples:

• Mineralocorticoid Receptor Antagonists for edema due to liver cirrhosis and for heart failure (spironolactone [Aldactone®])

• Estrogen Receptor Antagonists for the prevention and treatment of breast cancer (tamoxifen [Nolvadex®])
HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

• Antagonists of Nuclear Receptors

• Enzyme Inhibitors

• Ion Channel Blockers

• Transport Inhibitors

• Inhibitors of Signal Transduction Proteins
HOW DO DRUGS WORK BY INHIBITING ENZYMES?

Active Enzyme

Substrate ▶ Product

Cellular Function

Inactive Enzyme

Substrate ▶ Bound Enzyme

Inhibitor (Drug)
HOW DO DRUGS WORK BY INHIBITING ENZYMES?

KEY CONCEPTS:

Enzymes catalyze the biosynthesis of products from substrates.

- Some drugs bind to enzymes and inhibit enzymatic activity.

- Loss of product due to enzyme inhibition mediates the effects of enzyme inhibitors.
ARE DRUGS THAT INHIBIT ENZYMES CLINICALLY USEFUL?

Some important examples:

• Cyclooxygenase Inhibitors for pain relief, particularly due to arthritis (aspirin; ibuprofen [Motrin®])

HMG-CoA Reductase Inhibitors for hypercholesterolemia (atorvastatin [Lipitor®]; pravastatin [Pravachol®])

Angiotensin Converting Enzyme (ACE) Inhibitors for high blood pressure, heart failure, and chronic renal insufficiency (captopril [Capoten®]; ramipril [Altace®])
HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

- Antagonists of Cell Surface Receptors
- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins
ARE DRUGS THAT BLOCK ION CHANNELS CLINICALLY USEFUL?

Some important examples:

Calcium Channel Blockers (CCBs) for angina and high blood pressure (amlodipine [Norvasc®]; diltiazem [Cardizem®])

- Sodium Channel Blockers to suppress cardiac arrhythmias (lidocaine [Xylocaine®]; amiodarone [Cordarone®])
HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

• Antagonists of Nuclear Receptors

• Enzyme Inhibitors

• Ion Channel Blockers

• Transport Inhibitors

• Inhibitors of Signal Transduction Proteins
ARE DRUGS THAT INHIBIT TRANSPORTERS CLINICALLY USEFUL?

Some important examples:

Selective Serotonin Reuptake Inhibitors (SSRIs) for the treatment of depression (fluoxetine [Prozac®]; fluvoxamine [Luvox®])

Inhibitors of Na-2Cl-K Symporter (Loop Diuretics) in renal epithelial cells to increase urine and sodium output for the treatment of edema (furosemide [Lasix®]; bumetanide [Bumex®])
HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

• Antagonists of Nuclear Receptors

• Enzyme Inhibitors

• Ion Channel Blockers

• Transport Inhibitors

• Inhibitors of Signal Transduction Proteins
ARE DRUGS THAT INHIBIT SIGNAL TRANSDUCTION PROTEINS CLINICALLY USEFUL?

Some important examples:

Tyrosine Kinase Inhibitors for chronic myelocytic leukemia (imatinib [Gleevec®])

Type 5 Phosphodiesterase Inhibitors for erectile dysfunction (sildenafil [Viagra®])

- This is a major focus of drug development
HOW DO DRUGS WORK BY ACTIVATING ENDOGENOUS PROTEINS?

Agonists of Cell Surface Receptors
(e.g. alpha-agonists, morphine agonists)

• Agonists of Nuclear Receptors
(e.g. HRT for menopause, steroids for inflammation)

• Enzyme Activators
(e.g. nitroglycerine (guanylyl cyclase), pralidoxime)

• Ion Channel Openers
(e.g. minoxidil (K) and alprazolam (Cl))
HOW DO CHEMICALS WORK BY ACTIVATING CELL SURFACE RECEPTORS?

KEY CONCEPTS:

• Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.

• Some chemicals bind to cell surface receptors and trigger a response.

• Chemicals in this group are called receptor agonists.

• Some agonists are actually the endogenous chemical signal, whereas other agonists mimic endogenous chemical signals.
HOW DO CHEMICALS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION?

• Disrupting of Structural Proteins  
  *e.g.* vinca alkaloids for cancer, colchicine for gout

• Being Enzymes  
  *e.g.* streptokinase for thrombolysis

• Covalently Linking to Macromolecules  
  *e.g.* cyclophosphamide for cancer

• Reacting Chemically with Small Molecules  
  *e.g.* antacids for increased acidity

• Binding Free Molecules or Atoms  
  *e.g.* drugs for heavy metal poisoning, infliximab (anti-TNF)
• Being Nutrients
e.g. vitamins, minerals

• Exerting Actions Due to Physical Properties
e.g. mannitol (osmotic diuretic), laxatives

• Working Via an Antisense Action
e.g. fomivirsen for CMV retininitis in AIDS

• Being Antigens
e.g. vaccines

• Having Unknown Mechanisms of Action
e.g. general anesthetics
Receptors are an Excellent Drug Target

- Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.
- Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing:
  - **Specificity**: Only a subset of receptors will be targets
  - **Selectivity**: Since receptors are coupled to specific signaling pathways
  - **Sensitivity**: Receptor binding events are amplified intracellularly
### Signaling pathway

#### RECEPTION
- Binding of epinephrine to G protein-linked receptor

#### TRANSDUCTION
- Inactive G protein
- Active G protein
- Inactive adenylyl cyclase
- Active adenylyl cyclase
- ATP
- Cyclic AMP
- Inactive protein kinase A
- Active protein kinase A
- Inactive phosphorylase kinase
- Active phosphorylase kinase
- Inactive glycogen phosphorylase
- Active glycogen phosphorylase

#### RESPONSE
- Glycogen
- Glucose-1-phosphate

#### Number of molecules activated
- 1 molecule
- $10^2$ molecules
- $10^2$ molecules
- $10^4$ molecules
- $10^4$ molecules
- $10^5$ molecules
- $10^6$ molecules
- $10^8$ molecules