Chapter 2

Drug Receptors & Pharmacodynamics
Pharmacology

what the drug does to the body
 drug action/effect

Drugs → Body

pharmacodynamics

what the body does to the drug
 metabolism

pharmacokinetics
Pharmocodynamic Phase

- Processes of drug action that occur when drug reaches site of action and produces an effect.
Action vs. Effect

- **action** = how the drug works
  - usually by enhancing or inhibiting cell function

- **effect** = consequence of drug action on body
Example: Aspirin

action → block prostaglandin synthesis

effect → analgesia & antipyresis
How drugs act

- Many drugs exert their actions by binding to protein targets on mammalian cells
  - Receptors
  - Ion channels
  - Enzymes
  - Carrier molecules

- However there are exceptions
  - Antibiotics
  - Anti-cancer drugs
  - Etc
Drug ↔ Receptor Interaction

primary way drugs produce an action
RECEPTOR

- The component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug’s observed effects.

- The receptor concept, extended to endocrinology, immunology, and molecular biology, has proved essential for explaining many aspects of biologic regulation.
Receptor and Drug in Therapy

- Receptors largely determine the quantitative relations between dose or concentration of drug and pharmacologic effects
- Receptors are responsible for selectivity of drug action
- Receptors mediate the actions of both pharmacologic agonists and antagonists
  - Agonists activate the receptor to signal as a direct result of binding to it
  - Antagonists bind to receptors but do not activate generation of a signal
Model of Drug/Receptor Binding

Lock and Key
Receptor Types
Function and structure of receptors

- Drugs exert their effects via binding to receptors and induce biological responses.

- Binding the appropriate ligand and propagating its regulatory signal in the target cell

- Ligand-binding domain and effector domain
Several biologic signals are sufficiently lipid-soluble to cross the plasma membrane and act on intracellular receptors.

The ligands include steroids, sex steroids, vitamin D, and thyroid hormone.
Therapeutical consequences of intracellular receptors

- All of these hormones (ligands) produce their effects after a period of 30 minutes to several hours
- The effects of these agents can persist for hours or days after the agonist concentration has been reduced to zero
Ligand-Regulated Transmembrane Enzymes Including Receptor Tyrosine Kinases

- Be composed of an extracellular ligand-binding domain and a cytoplasmic enzyme domain (protein tyrosine /serine (threonine) kinase or a guanylyl cyclase)
- Insulin, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and many other trophic hormones.
- Ligand bind, conformation change, receptors bind to one another, tyrosine residues cross-phosphorylated
- Activated receptors catalyze phosphorylation of tyrosine residues in their substrates
The substrate of insulin receptor

TPK domain

Insulin binding site

membrane

insulin

ATP

ADP

Biological effect

IRS-1

Tyr

Tyr—P
Inhibitors of receptor tyrosine kinases are finding increased use in neoplastic disorders.

- Ligand binding often induces accelerated endocytosis of receptors from the cell surface and degradation (down-regulation).

**Therapeutical consequences**
Ligand-Gated Channels

- The open of channel results in the flow of ion and thereby alters the electrical potential across the membrane.

- The natural ligands including N-acetylcholine, excitatory amino acids (glycine, glutamate, etc), γ-GABA (Cl-, chlorine).

- All of these agents are synaptic transmitters.
Ligand-Gated Channels

- The time scale of signaling is about milliseconds
- The rapidity of this signaling is crucially important for moment transfer of information across synapses
G-protein-coupled Receptors

- This is the largest receptors family with over a hundred members cloned to date.
- G-protein: a kind of GTP-binding proteins with subunit of $\alpha \beta \gamma$
- Characteristics: seven-times crossing the plasma membrane, use G protein as transducers to convey signal to their effector proteins
G-protein-coupled Receptors

- **Members**: include receptors for many biogenic amines, such as adrenalin, DA, histamine, M-acetylcholine, and others.

- **G-protein-regulated effectors** include enzymes such as adenylyl cyclase and phospholipase C and plasma membrane ion channels.
G-protein-coupled receptors
Mechanisms of G-protein-coupled receptors
Well-Established Second Messengers

- The small molecule metabolite or ion
- Second messengers can diffuse through a cell and convey information to a wide variety of targets
- Well-studied second messengers include cyclic AMP and cyclic GMP, Ca$^{2+}$, phosphoinositides, and nitric oxide
A. Cyclic AMP

- Is the prototypical second messenger
- Is synthesized by adenylyl cyclase under the control of many G protein-coupled receptors
  - The activity of adenylyl cyclase can be modulated by phosphorylation and other regulatory influences
- Is eliminated by a combination of hydrolysis, catalyzed by phosphodiesterases, and extrusion by several plasma membrane transport proteins

\[
\text{adenyl cyclase (AC)} \quad \text{Phosphodiesterase (PDE)}
\]

\[
\text{ATP} \quad \text{cAMP} \quad 5’-\text{AMP}
\]
A. Cyclic AMP

- Activate cyclic AMP-dependent protein kinases
  - These kinases are composed of a cAMP-binding domain and catalytic chains
  - The PKA can phosphorylate both final physiological targets and numerous protein kinases and other regulatory proteins, including transcription factors
  - Regulate gene expression
cAMP

Inactive PKA → active PKA

Inactive phosphatases kinase → active phosphatases kinase

Inactive hepin phosphatases → active hepin phosphatases

Hepatin → 1-phosphate glucose
B. Calcium and Phosphoinositides

- Phospholipase C splits the phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP3).
- DAG is confined to the membrane and activates a phospholipid- and calcium-sensitive protein kinase called protein kinase C.
- IP3 triggers release of Ca2+ from internal storage vesicles.
C. Cyclic GMP

- In only a few cell types
- The cGMP-based signal transduction mechanism closely parallels the cAMP-mediated signal mechanism
- The NO-cGMP pathway
Features of signal transduction

- **Integration**: receptors, effectors, and transducers coordinate signals from multiple ligands with each other and with the metabolic activities of the cell.

- **Amplification**: catalytic nature when the receptor itself is an enzyme; a single agonist bind to an ion channel receptor; a single steroid hormone molecule binds to its receptor.
Theory and assumptions of drug-receptor interaction

- Binding to receptor causes some event which leads to the response.
- Response to a drug is graded or dose-dependent.
- For a given drug, the magnitude of response is directly proportional to the fraction of total receptor sites occupied by drug molecules (i.e. the occupancy assumption).
- The number of drug molecules is assumed to be much greater than the number of receptor sites.
Binding of drug with a receptor produces a specific response. "lock and key".

Drug-receptor interactions are analogous to enzyme-substrate interactions.

Endogenous ligands (e.g. enkephalin versus morphine).

Drugs without specific receptors (e.g. gaseous anesthetics).
Drug and receptor interaction

Drug receptor interaction follows simple mass-action relationships, i.e., only one drug molecule occupies each receptor site and binding is reversible. Can be described with Michaelis Menten equation:

\[
\begin{align*}
D + R & \rightleftharpoons DR \\
& \rightarrow \text{Effect}
\end{align*}
\]

\[
\begin{align*}
k_1 & \quad k_3 \\
D + R & \rightleftharpoons DR \\
k_2
\end{align*}
\]
Law of Mass Action

When a drug (D) combines with a receptor (R), it does so at a rate which is dependent on the concentration of the drug and the concentration of the receptor.

\[ \frac{k_1}{k_2} = \frac{[D][R]}{[DR]} \]

\[ K_D = \frac{[D][R]}{[DR]} \]

\[ K_A = \frac{1}{K_D} = \frac{k_1}{k_2} = \frac{[DR]}{[D][R]} \]

D = drug
R = receptor,
DR = drug-receptor complex
k_1 = rate for association and
k_2 = rate for dissociation.
K_D = Dissociation Constant
K_A = Association Constant
SATURATION CURVE

A. Total binding
B. Nonspecific binding
C. Difference = Specific binding
**SATURATION CURVE**

$\frac{\text{Specific Binding (fmol/mg)}}{[\text{DR}]}$

$[\text{Drug}] \text{ nM}$

$[\text{DR}]_{\text{max}}$

$R_T = B_{\text{max}}$

$k_2 = K_D = \frac{[\text{D}][\text{R}]}{[\text{DR}]}$

$k_1$

$R_T = \text{Total number of receptors}$

$B_{\text{max}} = \text{Maximal number of receptors Bound}$
**TIME COURSE**

Equilibrium

\[ K_D = \text{Equilibrium Dissociation Constant} \]

\[ k_2^- = K_D = \frac{[D][R]}{[DR]} \]

\[ k_1 \]

\[ [D] + [R] = [DR] \]

Equilibrium

\[ K_D = \text{Equilibrium Dissociation Constant} \]
SATURATION CURVE

At equilibrium, the dissociation constant is $K_D$ and the affinity is $K_A = 1/K_D$

Thus when $[D] = K_D$, half the total number of receptors will be occupied.
Terminology

Terms which indicate ability of drug to bind to receptor

- Potency
- Affinity (1/KD)
- $K_D$ or ED50

(Corresponds to $K_m$ in Michaelis-Menten analogy)
RELATION BETWEEN DRUG CONCENTRATION & RESPONSE

- D-E relationship of patient
- C-E relationship of in vitro system
Concentration-Effect Curves & Receptor Binding of Agonists

The relation between drug concentration and effect is described by a hyperbolic curve according to:

\[ E = \frac{E_{\text{max}} \times C}{C + EC_{50}} \]
If plotted the E versus log D or log C, the curve become typical symmetrical sigmoid curve.

Expands the low and compresses high concentration
Concentration-Bound Receptors

- Bmax indicates the total concentration of receptor sites
- Kd represents the concentration of free drug at which half-maximal binding is observed
- This constant characterizes the receptor’s affinity for binding the drug in a reciprocal fashion
- The EC50 and Kd may be identical, but need not be
Receptor-Effector Coupling & Spare Receptors

- The transduction process that links drug occupancy of receptors and pharmacologic response is often termed coupling.

- Receptors are said to be “spare” for a given pharmacologic response if it is possible to elicit a maximal biologic response at a concentration of agonist that does not result in occupancy of the full complement of available receptors.
Classification of Drugs

Antagonist

❖ A pure antagonist, which can bind to receptors without efficacy, antagonizes the biologic effects of the corresponding agonist.

Agonist

❖ Can bind to receptors, then activate receptors and produce pharmacological effect.
Agonist

- Agonist I drugs (direct agonists)
  - bind to same site as endogenous ligand
  - effect?
    - similar to ligand
Agonist

- Agonist II drugs (indirect agonists)
  - bind to different cell site
  - do not produce effect themselves
  - enhance effect of natural ligand
Competitive & Irreversible Antagonists

Antagonists are divided into two classes depending on whether or not they *reversibly compete* with agonists for binding to receptors.

- Competitive antagonist
- Noncompetitive/irreversible antagonist
Antagonist I

- competitive inhibitors: compete for same binding site
Competitive Inhibition

Log dose-response curves for a drug in the presence of increasing amounts of a competitive antagonist, A.
Competitive antagonist

- Competes the same receptor with agonist and reversibly binds to receptors
- The Emax for the agonist remains the same for any fixed concentration of antagonist
- The presence of antagonist will increase the ED50 of the agonist
- So the D-E curve of agonist will shift to the right.
Therapeutic Implications

- The degree of inhibition produced by a competitive antagonist depends on the concentration of antagonist. D → C
- Clinical response to a competitive antagonist depends on the concentration of agonist that is competing for binding to receptors
Non-competitive antagonist

- Irreversibly binds to receptors
- The antagonism can not be overcome by increasing the concentration of the agonist, that is to say the maximal effects of the agonist are depressed by the corresponding noncompetitive antagonist
- not only make the E-D curve of agonist move right, but also make the height of the curve descend.
noncompetitive inhibitors
bind to alternative cellular site and alter action of ligand
Noncompetitive Antagonist

Log dose-response curves for a drug in the presence of increasing amounts of a non-competitive antagonist.
Therapeutic Implications

- Therapeutically, irreversible antagonists present distinctive advantages and disadvantages.
- Consequently, the duration of action of such an irreversible antagonist is relatively independent of its own rate of elimination and more dependent on the rate of turnover of receptor molecules.
Partial Agonists

- Based on the maximal pharmacologic response that occurs when all receptors are occupied, agonist can be divided into two classes:

- Partial agonists produce a lower response, at full receptor occupancy, than do full agonists

The effects of full agonists can be considered more efficiently coupled to receptor occupancy than can the effects of partial agonists
Partial Agonists

- Partial agonists produce C-E curves that resemble those observed with full agonists in the presence of irreversible antagonists.
- The failure of partial agonists to produce a maximal response is not due to decreased affinity for binding to receptors (low intrinsic activity).
- Partial agonists competitively inhibit the responses produced by full agonists.
RELATION BETWEEN DRUG DOSE & CLINICAL RESPONSE

Dose-effect Relationship

- In a certain range of doses, the pharmacological response is increased in proportion with the increase in doses.

Dose-response curve

- The dose-effect curve can be obtained from plotting the pharmacological effect intensity (E) as y axis versus dosage (D) or concentration (C) of drugs as x axis.
Dose & Response in Patients

Graded response
- In a certain range of doses, the pharmacological response increases with the increasing of doses.
- blood pressure, muscle contraction, urinary excretion of sodium

Quantal response or all-or-none response
- Indicate that a given dose of a drug has or has not evoked a certain effect in the various subjects under investigation.
- Expressed with all or none, positive or negative, e.g., death or survival, convulsion or not, paralysis or not
Potency

- Refers to the concentration (EC\textsubscript{50}) or dose (ED\textsubscript{50}) of a drug required to produce 50\% of that drug’s maximal effect.

- What is mean more potent?

- Nitroglycerin is very potent; relatively few molecules need to be absorbed to produce the therapeutic effect.

- If the drug is to be administered by transdermal absorption, a highly potent drug is required, since the capacity of the skin to absorb drugs is limited.
SEMILOG DOSE-RESPONSE CURVE

- **EFFECT**: Contraction (mm)
- **Maximal Effect**
- **POTENCY**
- **ED50**
- **EFFICACY**

Log [Dose]
Maximal Efficacy

◆ The maximal effect that can be produced by a drug is its maximal efficacy. It reflects the limit of the dose-response relation on the response axis.

❖ The maximal efficacy of a drug for achieving a therapeutic end point may be limited by the drug’s propensity to cause a toxic effect even if the drug could otherwise produce a greater therapeutic effect.
Efficacy: $A = B < C$

Potency: $A > B > C$
QUANTAL DOSE-EFFECT CURVES

- When these responses are summated, the resulting cumulative frequency distribution constitutes a quantal dose-effect curve.

- In this curve, the proportion or percentage of individuals who exhibit the effect plotted as a function of log dose.
Quantal Dose-response Curves

Cumulative distribution of population responding to drug A
Quantal Dose-response Curves

Frequency of distribution
% population responding to drug A
The difference between graded and quantal responses and their dose-effect curves

- Both curves provide information regarding the potency and selectivity of drugs
- ED50 or EC50
- The graded dose-effect curve indicates the maximal efficacy of a drug
- The quantal dose-effect curve indicates the potential variability of responsiveness among individuals.
Biological Variability

- The middle of this curve between 20%-80% effect shows the linear characteristic, that means the slight increasing or decreasing of the dosage will result in a more sensitive changing of the proportion or percentage of individuals who exhibit the effect.

- The steep slope of the quantal dose-effect curve indicates little individual variability.
Median effect dose (ED$_{50}$)

- For all-or-none responses, the dose of a drug that gives rise to a response in 50% of the subjects is called ED$_{50}$
- It provides a convenient way of comparing the potencies of drugs in experimental and clinical settings
Meanings of \(ED_{50}\)

- If the ED50s of two drugs for producing a specified quantal effect are 5 and 500 mg, respectively, then

- One can obtain a valuable index of the selectivity of a drug’s action by comparing its ED50s for two different quantal effects in a population
  - Eg, cough suppression versus sedation for opioid drugs
Median lethal dose (LD50)

- A dose that gives rise to the death of 50% of subjects is called LD50
- LD50 is a primary index evaluated the safety of a drug, but it can not reflect the relationship between drug effect and toxic effect.
Therapeutic index (TI)

- Is a measure which relates the dose of a drug required to produce a desired effect to that which produces an undesired effect
- Denotes the safety of the drugs
- $\text{TI} = \frac{\text{LD}_{50}}{\text{ED}_{50}} \quad (\frac{\text{LC}_{50}}{\text{EC}_{50}})$

The larger value of the TI is, the wider margin between effective dose and toxic dose is. For example, the drug of TI=4 is more safe than that of TI=2.