What the drug does to the body
Pharmacodynamics, PD

Drug Action and Mechanism

Absorption, Distribution, Metabolism, Excretion

Pharmacokinetics, PK
What the body does to the drug
PHARMACODYNAMICS

Receptors
- intracellular receptors
- membrane receptors
  - Channel receptors
  - G protein-coupled receptors
  - Tyrosine-kinase receptors

Drug/receptor interactions
- agonists and antagonists
- potency and efficacy (effectiveness)
- therapeutic index

Drug effects
- therapeutic effects
- side effects
- toxic effects
DRUG/RECEPTOR INTERACTION

Drugs can interact with receptors through a variety of chemical interactions including:

• **Electrostatic interactions**  
  (hydrogen bonds, Van der Waals forces) - the most common mechanism.

• **Hydrophobic interactions**  
  (important for lipid soluble drugs).

• **Covalent bonds**  
  (e.g. phenoxybenzamine binding to α-adrenergic receptors) - least common

• **Stereospecific interactions**  
  (>50% of drugs exist as stereoisomers and interact stereospecifically with receptors. e.g. S (-) Carvedilol binds to both α-adrenergic receptors and β-adrenergic receptors, whereas R(+) Carvedilol binds selectively to α-adrenergic receptors).
AGONISTs and ANTAGONISTs

The endogenous ligand binds to receptor and produces an effect.

An agonist drug has an active site of similar shape to the endogenous ligand so binds to the receptor and produces the same effect.

An antagonist drug is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and so prevents the endogenous ligand from binding.
AGONISTS and ANTAGONISTs

AGONIST = An agonist is a chemical that binds to a receptor and activates the receptor to produce a biological response (AFFINITY and INTRINSIC ACTIVITY)

ANTAGONIST = An antagonist is chemical that has AFFINITY but NO EFFICACY for its cognate receptor. Therefore binding will disrupt the interaction and inhibit the function of an agonist at receptors.
LIGAND/RECEPTOR INTERACTION: the whole spectrum
POTENCY and EFFICACY

The degree of biological activity is proportional to the amount of active drug/receptor complexes. A drug’s effect can be evaluated in terms of potency and efficacy.

**POTENCY** (strength) refers to the amount of drug needed to produce an effect (for example, relief of pain or reduction of blood pressure).

**EFFICACY** is a drug's capacity to produce an effect (such as lowering blood pressure).

*Effectiveness* differs from efficacy in that it takes into account how well a drug works in real-world use. For example, a drug may have high efficacy in lowering blood pressure but may have low effectiveness because it causes so many side effects that people take it less often than they should or stop taking it entirely. Thus, effectiveness tends to be lower than efficacy.
POTENCY and EFFICACY

POTENCY = $\text{ED}_{50}$ (Effective Dose 50), $\text{EC}_{50}$ (Effective Concentration 50)

$\text{ED}_{50}$: the drug dose producing 50% of a maximal effect; or alternatively the dose producing the desired effect in 50% of the population. Which definition is appropriate depends on the context in which the abbreviation is being applied; i.e., referring to the results of a population study, or drug effects on a single animal).

EFFICACY = $E_{\text{max}}$ (maximal effect)

$(E_{\text{max}})$ is the maximum response achievable from a drug.

![Graphs showing potency and efficacy comparison between drugs A, B, C, and D.](image)
DOSE-RESPONSE CURVE

Therapeutic effect (%)

Concentration of the drug (logarithmic scale)

ED$_{50}$

Dose determining 50% of maximal effects
OR
dose achieving maximal effect in 50% of population

Drug concentration

(ED$_{50}$)
The lower the EC50, the higher the drug potency (less drug to obtain the expected effect).

The higher the Emax, the higher the efficacy of the drug to modify the biological activity considered.
POTENCY and EFFICACY

WHICH DRUG HAS THE HIGHEST POTENCY?
Partial agonists are drugs that bind to and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist.

**FULL AGONIST**

The full agonist can induce a conformational change in the receptor leading to a maximal effect. The ability to induce changes in the receptor conformation leading to activation is a measure of the intrinsic activity.

**PARTIAL AGONIST**

Partial agonists can induce some degree of receptor activation but not of sufficient magnitude for a maximal response.
Partial agonists are drugs that bind to and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist.

Partial agonists may behave as antagonists.
**PARTIAL AGONISTs**

**Partial agonists** have full affinity for the receptor active site but weak efficacy in receptor activation (with respect to a full agonist).

If **NO FULL AGONIST** is present, a **PARTIAL AGONIST** produces some response.

If **PARTIAL** and **FULL AGONIST** are present, then less full agonist can bind, and therefore total response is less (acts as an antagonist).
ANTAGONISTs

ANTAGONIST = An antagonist is a chemical that has **affinity but no efficacy** for its cognate receptor. Therefore binding will disrupt the interaction and inhibit the function of an agonist at receptors.
COMPETITIVE and NON-COMPETITIVE ANTAGONISTs

**Competitive antagonists** bind reversibly to the same receptor site as the agonist.

**Noncompetitive antagonists** either bind *irreversibly* (e.g. by covalent bonds) to the same site as the agonist, or bind to a different site which reduces the binding of the agonist by an *allosteric* mechanism.
A receptor is characterized by a
- LIGAND BINDING SITE (ACTIVE SITE)

Several receptors may also present a
- ALLOSTERIC REGULATORY SITE

ALLOSTERIC REGULATION of a receptor results from the binding of allosteric modulators at a site (a "regulatory site") different from that of the endogenous ligand (the "active site"). This allosteric binding enhances or inhibits the effects of the endogenous ligand.

Under normal circumstances, the allosteric binding acts by causing a conformational change in a receptor molecule, which results in a change in the binding affinity of the ligand.
COMPETITIVE and NON-COMPETITIVE ANTAGONISTS

Effect (%)

Agonist dose (Log scale)

Agonist alone

Agonist + competitive antagonist

Effect of antagonist

Agonist + noncompetitive antagonist
**COMPETITIVE and NON-COMPETITIVE ANTAGONISTS**

### Competitive antagonists:
Their inhibitory effects can be “surmounted” by addition of a higher concentration of agonist. This effect produces a rightward parallel shift of the dose-response for the agonist. In the presence of a competitive antagonist, agonists can still produce the same (e.g. 100%) maximal effect, but higher agonist concentrations are needed to produce the same level of effect.

### Noncompetitive antagonists:
The primary effect of a noncompetitive antagonist is a reduction in the maximal effect produced by the agonist. (In some cases the slope may also be reduced.) In contrast to a competitive antagonist, the effect of a noncompetitive antagonist cannot be reversed by simply increasing the concentration of the agonist, since the law of mass action does not apply.
VARIOUS TYPES OF ANTAGONISM

• **A) Physical Antagonism** - Based on physical property of drugs, e.g. charcoal (adsorb alkaloid) in alkaloidal poisoning

• **B) Chemical Antagonism** - A type of antagonism where a drug counters the effect of another by simple chemical reaction / neutralization (not binding to the receptor) e.g. Calcium sodium edetate form insoluble complexes with arsenic / lead

• **C) Functional Antagonism** - (Physiological Antagonism) Opposite effects of two drugs on same function: two drugs act on two different types of receptors AS AGONISTS, but each drug antagonizes action of each other e.g. Glucagon and insulin on blood sugar level

• **D) Pharmacological Antagonism** - Competitive Non-competitive Equilibrium Non-equilibrium (Reversible) (Irreversible)
**LETHAL DOSE - TOXIC RESPONSE CURVE**

TOXIC EFFECT (%)

Drug Concentration (Log scale)

**TD<sub>50</sub>**

Dose producing death in 50% of cases

(TD<sub>50</sub>)
The **therapeutic index** (TI) is a measure of drug safety. It results from the comparison of the **amount of a therapeutic** agent that causes the therapeutic effect to the **amount that causes toxicity**.

\[
\text{TI} = \frac{\text{Median Toxic Dose}}{\text{Median Effective Dose}} = \frac{\text{TD50}}{\text{ED50}}
\]

**Low THERAPEUTIC INDEX:** risky drug: doses necessary to obtain the therapeutic effect are very close to doses responsible for toxic effect. A minimum variation may shift the balance toward toxicity.

**High THERAPEUTIC INDEX:** relatively “safe” drug. Even when high doses are administered, they are far below those inducing toxicity.
THERAPEUTIC WINDOW

ED90 = LD15

DRUG CONCENTRATION (log scale)
THERAPEUTIC WINDOW

The larger the TI, the less likelihood for overlap between the dose-response curves for therapeutic & toxic side effects, and the safer the drug.

Example: \( IT = 10 \rightarrow \frac{TD50}{ED50} \rightarrow \frac{10}{1} \)

A dose 10 times higher than \( ED_{50} \) causes toxic (lethal) effects in 50% of cases.
PLASMATIC DRUG CONCENTRATION – RESPONSE CURVE
DRUG-DRUG INTERACTION

Drugs may interact with each other in “agonistic” or antagonistic ways. Two common types of “agonistic” drug interactions are additive or synergistic interactions.

When two drugs with similar mechanisms are given together, they typically produce additive effects. This is also referred to as summation.

If the effect of two drugs exceeds the sum of their individual effects, this is referred to as potentiation or synergism. Potentiation requires that the drugs act at different receptors or effector systems.