Pharmacology 659

Dose-Response Relationships

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Concentration-Effect Relationships

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Types of Dose-Response Relationships

• **Graded**, when responses of an organ or tissue are determined in the presence of increasing concentrations of a drug

• **Quantal**, when an “all-or-none” response of an individual patient is determined in the presence of increasing concentrations of a drug
Graded Dose-Response Relationships
Law of Mass Action

\[ [D] + [R] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [D\cdot R] \]

Response
EC\(_{50}\)
**Efficacy** (intrinsic activity) – the property of a drug that determines the magnitude of the response the results from the drug-receptor combination.

**Potency** – a measure of the affinity of a drug for the receptor with which it combines. The higher the affinity of a drug for its receptor, the greater the potency of the drug.

**Relative Potency** – the potency of a drug when compared with the potency of another drug that is used for the sake of comparison.
The graph illustrates the relationship between the logarithm of the agonist concentration (log [AGONIST]) and the percentage of maximal effect (% OF MAXIMAL EFFECT). The curve reaches 50% effect at a certain concentration, which is the EC₅₀ (effective concentration). The graph also shows the correlation with efficiency (Efficiency) and potency (Potency).
Drug Antagonism

1. Chemical
2. Competitive
3. Noncompetitive
4. Physiological
Chemical Antagonism

If a drug reacts chemically with an agonist to form a product that cannot activate a receptor, then it is referred to as a chemical antagonist.
Drug Antagonism

[agonist] X

[antagonist] Y

Receptor

Competitive Reversible

Response
Competitive Reversible Antagonism

The condition in which the agonist and antagonist bind reversibly to the same recognition sites on the receptor, and thus when present concomitantly compete for such sites, is called competitive reversible antagonism.
Log [AGONIST] vs. % of maximal effect. Agonist alone and agonist plus increasing concentrations of a competitive antagonist.
pA₂

The negative logarithm of the concentration of antagonist necessary to cause a two-fold shift to the right in the agonist concentration-effect curve.
Schild Plot

Log [Dose Ratio – 1] vs. log [ANTAGONIST]

Dose Ratio with EC50

Slope = 1 for competitive antagonist

KD antagonist

EC50 with antagonist

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Noncompetitive Antagonism

In this condition the antagonist interacts with a binding site intimately associated with the receptor, but distinct from the site for agonist binding, and causes a change in the receptor site such that the agonist can no longer bind to the receptor.
Irreversible Antagonism

In this condition the antagonist binds irreversibly to either the receptor or to some other site which causes the receptor to no longer bind with the agonist.
Drug Antagonism

1. Irreversible
2. Noncompetitive

Response
**AGONIST**

![Graph showing the effect of an agonist alone and with an irreversible or non-competitive antagonist](image-url)

- **Agonist alone**
- **Agonist plus irreversible or non-competitive antagonist**
Spare Receptors
log $\text{AGONIST}$

% OF MAXIMAL EFFECT

$0$ $50$ $100$
log [AGONIST]
Addition occurs when the effect of two drugs given together is the sum of the effects of each of the drugs when given alone.

Synergism occurs when the effect of two drugs given together is greater than the sum of the effects of each of the drugs when given alone.
Quantal Dose-Response Relationships
log [AGONIST]

% OF INDIVIDUALS RESPONDING

hypnosis
dead

EC$_{50}$
LD$_{1}$
EC$_{99}$
LD$_{50}$
Therapeutic Index

Therapeutic Index = \frac{LD_{50}}{ED_{50}}

The greater the therapeutic index, the safer the drug!