General Pharmacology
(Pharmacodynamic III)
Principles of Pharmacology
(PP IV)

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• **References:**

• Basic & clinical pharmacology by Katzung
• Lippincott’s illustrated reviews by Finkel, Cubeddu & Clark
• Clinical pharmacology by Laurence
4. Describe what is meant by the terms ‘efficacy’ and ‘affinity’ in describing agonist potency and how these relate to the concepts of ‘spare receptors’ and ‘partial agonists’.
• **Dose-response relationships**

• **AGONIST DRUG:**

• "An agent that can bind to a receptor producing a biological response".

• The magnitude of the drug effect depends on the drug's concentration at the receptor site (determined by the dose of drug administrated and by factors characterized of the drug kinetic profile. i.e. the rate of absorption, distribution and metabolism."
Learning Objectives
At the end of pharmacodynamic lectures you should be able to

1. Describe the relationship between drug dose and response, and between log (drug dose) and response

2. Define ‘competitive’ and ‘non-competitive’ antagonism, and indicate, on appropriate graphs, how these may be distinguished

3. Describe the different types of receptor-effectors coupling with reference to: a) ion channels; b) second messengers; c) protein kinases; and d) intracellular receptors
Characteristics:

1) A drug that interacts with a receptor.
2) Causes a response.
3) It has affinity for the receptor.
4) It has efficacy (intrinsic activity).
5) It has "fast" rate of association and dissociation from the receptor.
• Agonist drugs are known to activate receptors because they resemble the natural transmitters or hormones.

• Their importance depends on their capacity to resist degradation inside the body and to act for longer than the natural substances they mimic. For example: Bronchodilation produced by "salbutamol" lasts longer than that induced by "adrenaline".
GRADED DOSE RESPONSE RELATION:

As the concentration of a drug increased, the magnitude of its pharmalogical effect also increases. The relationship between dose and response is a continuous one:

- \([\text{drug}] + [\text{receptor}] \rightarrow [\text{drug-receptor complex}]\]

- The response is a graded effect (continuous and gradual).
• **POTENCY:**

• A measure of the amount of drug necessary to produce an effect of a given magnitude.

• The concentration producing an effect that is 50% of the maximum is used to determine potency; it commonly designated as the "EC$_{50}$" as the diagram below shows;
• The EC$_{50}$ is the concentration of the drug that produces a response equal to 50% of the maximum response.

• The EC$_{50}$ for drugs A and B are indicated (Drug A is more potent than Drug B) because less dose of drug A is needed to obtain 50% effect.
• **AFFINITY AND INTRINSIC ACTIVITY (EFFICACY):**
  • The magnitude of the response is the function of number of receptors occupied.

• **AFFINITY**
  • "Is the tendency of a drug to form a combination with the receptor".
  • The response is not only the function of concentration of drug-receptor complex but it also depends on the intrinsic activity or "efficacy".

• **EFFICACY**
  • "Is the capacity to stimulate for a given receptor occupancy"
Log dose-response curves showing the difference between potency and efficacy.

Panel A: drug A is much more potent than drug B but both have the same maximum response.
Panel B: drug A is not only more potent but also has a greater efficacy (higher Peak Effect) than drug B.
• **ANTAGONISTS:**
  • "Are drugs that decrease the activity of another drug or endogenous ligand".

• **Characteristics:**
  • 1) A compound or a drug that interacts with receptors preventing the action of agonist.
  • 2) Produces very small or no response.
  • 3) It has affinity for receptors.
  • 4) It has NO efficacy.
  • 5) Slow rate of association and dissociation

• Antagonists are similar to some extent to the natural agonists to be recognized by receptors and to occupy these receptors without activating them, thereby preventing (blocking) the natural agonist from exerting its effect.
**PARTIAL AGONIST:**

1) Agents (drugs) act on the same receptors as powerful agonists.
2) Do NOT produce the same maximum effect regardless of their concentration.
3) Have HIGH affinity.
4) Have LOW efficacy.

Some drugs in addition to blocking access of the natural agonist to receptors are capable of low degree of activation. i.e. (have the action of both agonist and antagonist).
• **TYPES OF DRUG ANTAGONISM:**

• **1) PHARMACOLOGICAL ANTAGONISM:**
  • Antagonist competes with Agonist for the same receptor site so reducing or preventing the action of the Agonist.

  • Pharmacological Antagonism is further subdivided into:
    • **A) COMPETITIVE REVERSIBLE ANTAGONISM:**
      • In this case the antagonist combines "reversibly" with the receptor so this combination can be overcome by increasing the concentration of the agonist.

    • **B) NON-COMPETITIVE IRRVERSIBLE ANTAGONISM:**
      • Antagonist combines "irreversibly" with the receptor by a covalent bond so increasing the dose of agonist will (never) overcome the inhibition
2) **CHEMICAL ANTAGONISM:**
- A mechanism at which one drug antagonize the actions of a 2nd drug by binding to it and causes its inactivation.
- For example: "Protamine" a protein positively charged at physiological pH, can be used to counter the effects of "Heparin ", an anticoagulant negatively charged.

3) **PHYSIOLOGICAL (FUNCTIONAL) ANTAGONISM:**
- A mechanism at which one compound or drug opposes the physiological action of another drug.
- For example: "Glucocorticoid Hormones" increase blood sugar while "insulin" decrease it.
• **MEDIAN TOXIC DOSE (TD 50):**
  • "Is the dose required to produce a particular toxic effect in 50% of experimented animals".

• **MEDIAN LETHAL DOSE (LD 50):**
  • "Is the dose required to cause death to 50% of experimented animals",

• **THERAPEUTIC EFFICACY:**
  • "Is the capacity of a drug to produce an effect and refers to the maximum of such effect".
  • This means if drug A can produce a therapeutic effect that can’t be obtained by drug B however much of drug B is given then drug A has the higher therapeutic efficacy.
**THERAPEUTIC INDEX (TI):**

- "Is the ratio of the dose that causes toxicity to the dose that causes a clinically desired effect (response) in a population of individuals".

- Therapeutic Index = $TD_{50} / ED_{50}$

- Where, TD is the Toxic Dose
- ED is the Effective Dose
“THE GREATER THE INDEX, THE MORE SAFE IS THE DRUG” (TI) is a measure of the drugs' safety, because Larger Value of (TI) indicates a wide margin between doses that are effective and doses that are toxic.
**TOLERANCE:**

- A condition when developed, it becomes necessary to increase the dose of a drug to obtain an effect which is previously obtained by a smaller dose.

- Tolerance is either:

  - **NATURAL:**
    - It’s not induced by the drug but it happens due to "inherited factors" (Pharmacogenetic).
• **ACQUIRED:**
  • Which is developed after a prolonged time of using a drug, due to:

  • a) **Reduced efficacy at receptor sites** as with "opioids".
  • b) **Enzyme induction** (increased metabolism) as with "alcohol".
  • I.e. An increase in enzymes causes an increase in drug metabolism so the drug concentration is decreased, rapidly
  • c) **Cross- Tolerance** between drugs of similar structure or metabolized by the same enzyme, and sometimes between dissimilar drugs. For example: "Antibiotics".
Thank you