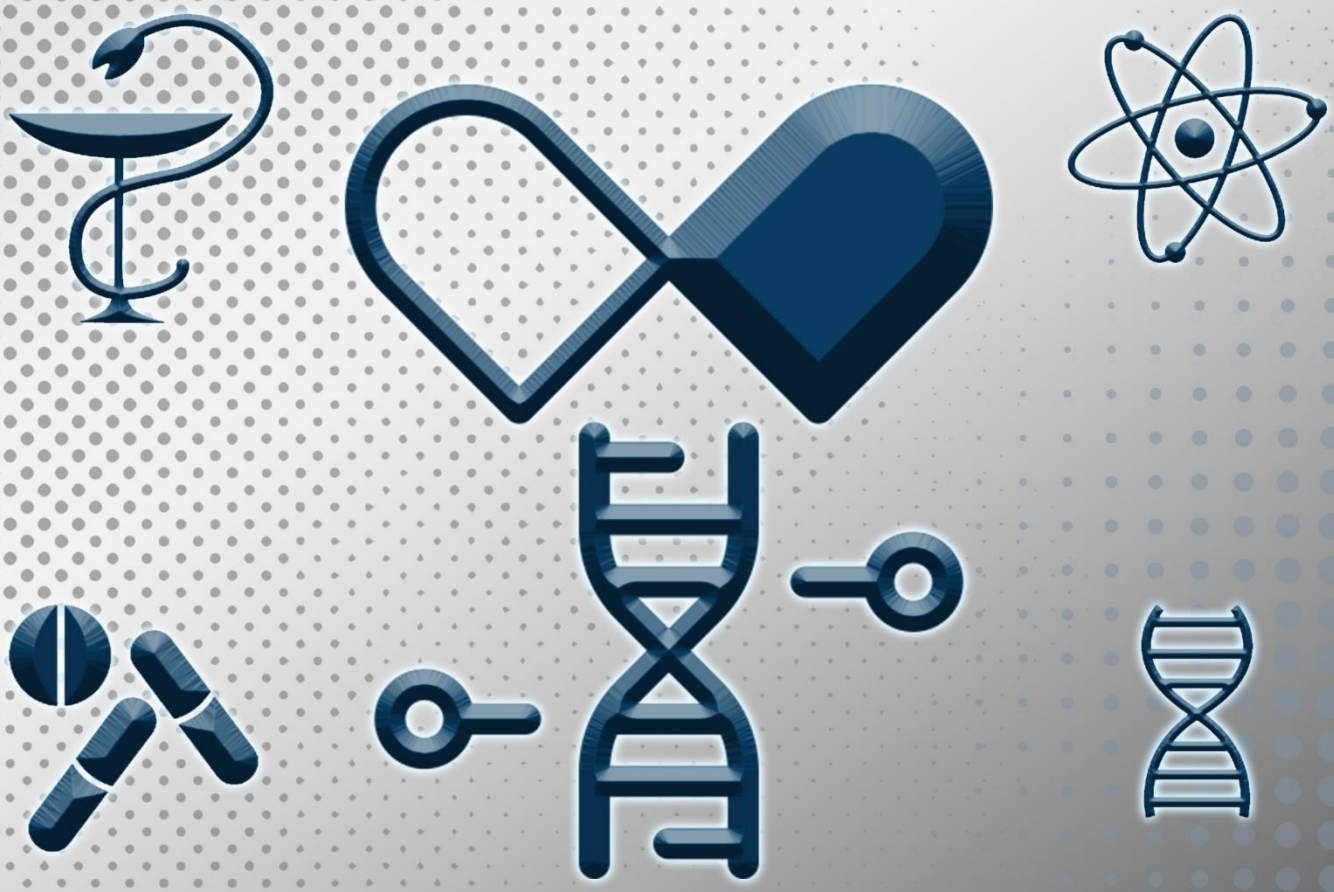
Pharmacology



Done By:

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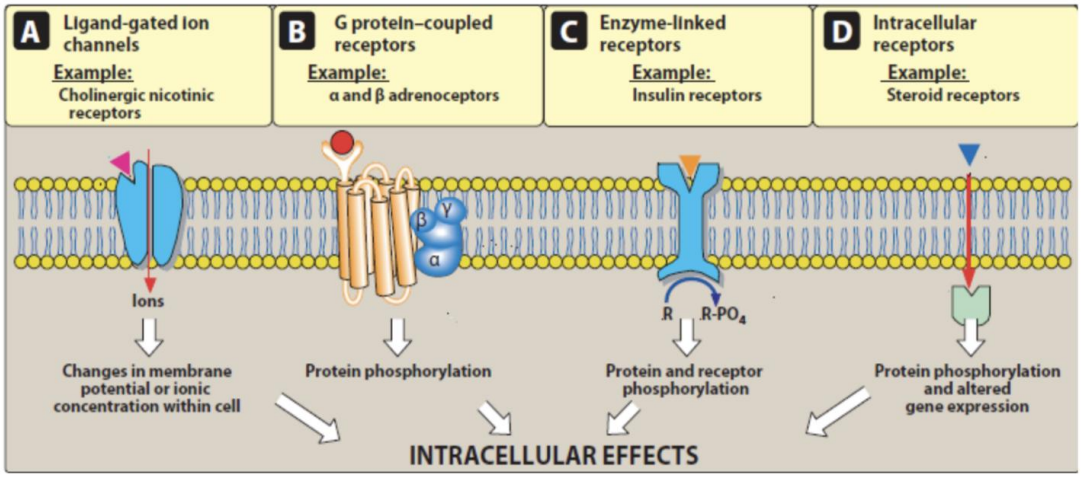
Drug Receptors & Pharmacodynamics

- The drug effects are achieved by drug receptor interaction that will lead to effect.
- This drug receptor interaction is called pharmacodynamics.
  - By afflicting the **receptor** → Changes the macromolecules' biophysical activities → Response.

- Receptor-Effector Coupling

- Receptor: Protein at the cell surface that is responsible for response.
- Ligand: It is the substance that binds to receptor to do the response (endogenous or exogenous).
  - When a ligand (Drug) occupies a receptor >> pharmacologic response **(coupling)**.
  - Mechanism:
    - ➔ The Drug is attached to receptor.
    - ➔ Conformational changes in the receptor,
    - ➔ Downstream biochemical events that produce receptor occupancy into cellular response.



  - The receptors have characteristics:
    - ➔ Specificity (Selectivity):
      - Each Receptor is specific for certain substance Depends on receptor binding site.
    - ➔ Saturation & Competition & Reversibility.
  - Structure of the receptor:
    - ➔ Extracellular domain:
      - Receptor binding site: certain region of receptor where the ligand binds.
    - ➔ Intracellular domain:
      - Where the conformational changes occur (3D arrangement changed).
      - Stimulates the formation of effectors, that initiates the response.

Receptors conformation:

- Active state (**Ra** conformation).
  - Can activate downstream mechanisms to produce a (constitutive activity), even when it empty, or increase in the cell activity.
- Inactive state (**Ri** conformation).
  - Produces no effect, even when combined with a drug molecule, or decrease in the cell activity.
- Basal "Constitutive activity":
  - In absence of any agonist, some receptors exist in **Ra form** and produce physiologic effect as agonist-induced activity.

- Types of ligands:
  - **Agonist:** activates the receptor by binding to its binding site.

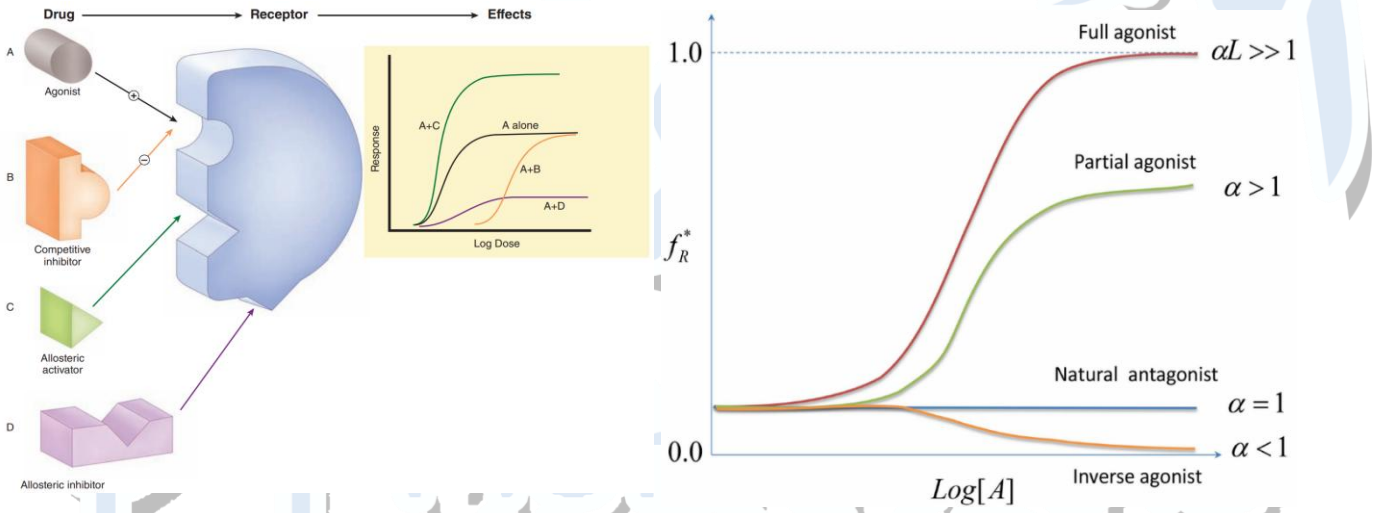
    Ra + D (*) → Ra*
  - **Antagonist (Neutral, Constitutive):** binds to receptor without activate it (↓agonist function).

    Ra + D (*) → Ra*, Ri + D (*) → Ri*

    → Has no effect on receptor (no activation or inhibition), the receptor activity (basal activity).
  - **Inverse Agonist:** Binds to receptor and inhibits it.

    Ri + D (*) → Ri*
  - **Partial Agonist:** Binds to receptor & activates it but not like agonist.

    Ra + D (*) → Ra*, Ri + D (*) → Ri*
  - **Allosteric Modulators:** creates a signal by binding to the receptor at a different binding site.
    - → Allosteric Activator: May increase the response of the agonists or its binding affinity.
      - Positive Allosteric Modulators: example is benzodiazepines.
    - → Allosteric Inhibition: May decrease the response of the agonists or its binding affinity.
      - Negative Allosteric Modulators.



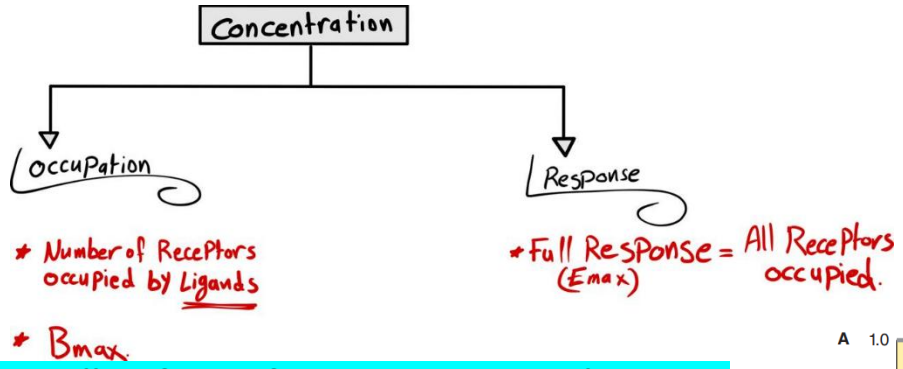
☒ Notes:
- Full agonist: Binds more to Ra (More affinity toward Ra & form Ra–D).
- Partial agonists: have an intermediate affinity for both Ri and Ra forms.
- Inverse agonist: Binds more to Ri (More affinity toward Ri), thus reduce basal activity.
- Antagonist: Has equal affinity to Ra & Ri, thus maintains the same level of basal activity.

- Receptor affinity of drug: Determine #drug-receptor complexes formed.

- Equilibrium of reaction:
  - Ra + D* ⇌ Ra-D (Ra*) → Stimulates the effectors → Response.
  - Ri + D* ⇌ Ri-D (Ri*) → No Stimulation of effectors → No response, diminished activity.

	Effect on Ra	Effect on Ri
Agonist:	Ra + D* ⇌ Ra-D (Ra*) = 100%	Ri + D* ⇌ Ri-D (Ri*) = 0%
Partial agonist:	Ra + D* ⇌ Ra-D (Ra*) = 70%	Ri + D* ⇌ Ri-D (Ri*) = 30%
Antagonist:	Ra + D* ⇌ Ra-D (Ra*) = 50%	Ri + D* ⇌ Ri-D (Ri*) = 50%
Inverse Agonist:	Ra + D* ⇌ Ra-D (Ra*) = 0%	Ri + D* ⇌ Ri-D (Ri*) = 100%

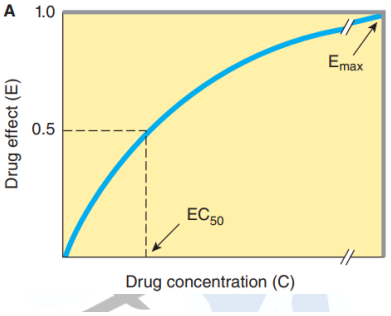
RELATION BETWEEN DRUG CONCENTRATION & RESPONSE



- Concentration-Effect Curves & Receptor Binding of Agonists

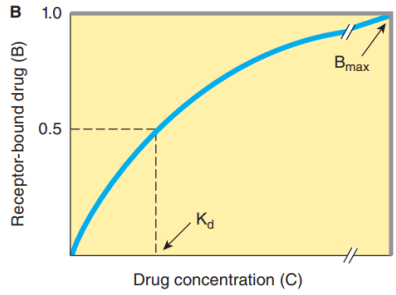
- Responses to low drug dose increase in direct proportion to dose.
- Then, the response becomes constant even if the dose increased.
- This described by a hyperbolic curve according to the equation:

$$E = \frac{E_{max} \times C}{C + EC_{50}}$$



- This suggests that drug agonists act by binding to a distinct class of biologic molecules with a characteristic affinity for drug receptor.
- Drug bound to receptors (B) relates to conc. of unbound drug (C) & described:

$$B = \frac{B_{max} \times C}{C + K_d}$$



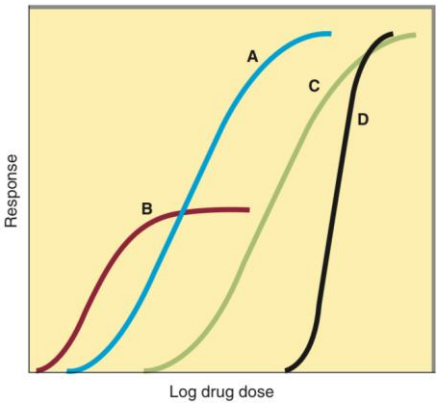
Kd (Constant of dissociation)	EC_{50}
Inversely proportional to Receptor's affinity	Drug Potency (drug amount needed for effect)
If the Kd is low, binding affinity is high	Low EC50 more potent drug
Drug concentration when **50% of drug is bound to receptors (Occupancy).**	Durg concentration when **50% of drug effect is observed**.
Determines number of occupied receptors at certain drug concentration.	
The EC50 and Kd may be identical but need not be	

☒ **Note: Efficacy of drug depends on the maximum effect (Emax).**

Dose & Response in Patients

- Graded Dose-Response Relations

- We must know the drug with best potency and maximal efficacy to the therapeutic effect.
- Potency
  - ➔ Concentration of a drug required to produce 50% of that drug's maximal effect = EC50.
  - ➔ It is the effect of drug per unit of weight (dosage units).
  - ➔ Relative potency, the ratio of equal-effective doses.
    - To determine the more potent drug.
      - ❖ $\frac{EC50\ of\ A}{EC50\ of\ B} = more\ than\ 1.$
      - ❖ Thus, EC50 of B is less than EC50 of A,
      - ❖ Drug B is more potent than A.



Notes:

☒ Drug B has the highest potency and the least efficacy.

☒ Potency is affected by:

➔ Number of receptors: more receptors thus rapid response (More potent).

➔ Affinity: more affinity thus rapid response (More potent).

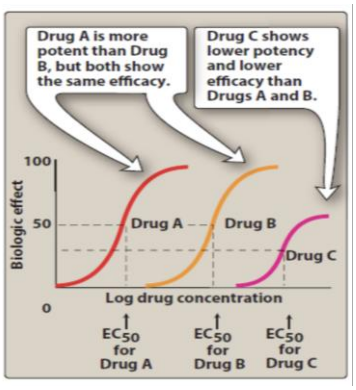
☒ If the question told you that number of receptor equal and ask about affinity then the drug with more affinity is the more potent drug and vice versa.

- Maximal efficacy "Emax"
  - ➔ The practical efficacy of a drug for achieving a therapeutic end point.
  - ➔ To have Emax all receptors (100% of receptors) must be occupied.

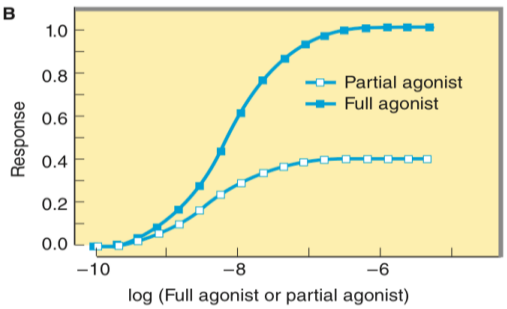
Very important

Efficacy	Potency
Maximum effect of drug (Emax).	Effect of drug at EC50
Decreased: shift curve down. **Increased: shift curve up.**	**Decreased: shift curve right.** **Increased: shift curve left.**

No relation between Efficacy & Potency.



- **Agonists:**
  - Agonists can be divided into:
    - ➔ Full agonists.
    - ➔ Partial agonists:
      - o Mixed "agonist-antagonist" property
      - o Produce a lower response, than do full agonists.
      - o Concentration-effect curves like that with presence of non-competitive antagonist.

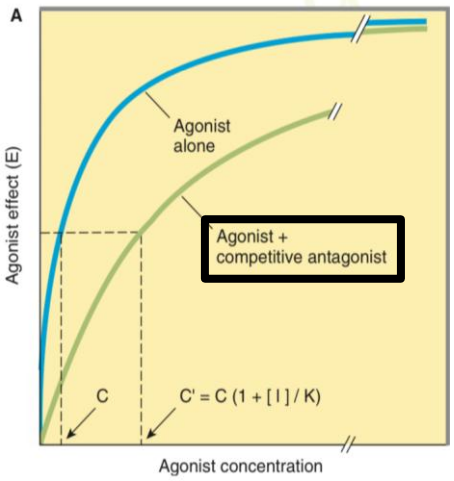


☒ Note: partial agonists fail to produce a maximal response is due to:

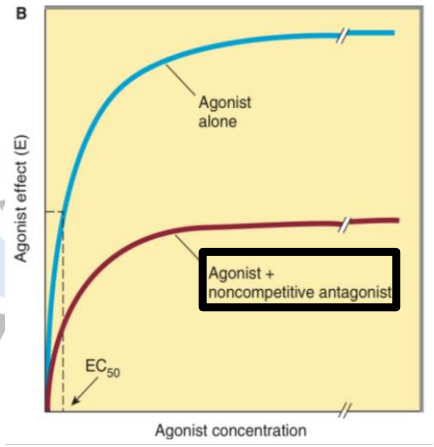
- They competitively inhibit the responses produced by full agonists.
- Not due to decreased affinity for binding to receptors (As book said).

- **Antagonists (Reversible & Irreversible)**
  - Receptor antagonists:
    - ➔ Bind to receptors but do not activate them (reduce the effects of agonists).
    - ➔ **Receptors have more affinity to Antagonists compared to Agonist.**
    - ➔ Then, when we combine Agonist and Antagonist
      - o Most Antagonist have no function in absence of agonists, but some inverse agonist.
        - ** We must combine agonist with antagonist to observe its effect.
        - ** No functional effect of antagonist in absence of agonist.
      - o Agonist binds to Ra leads to activation.

- Divided into:
  - ➔ **Competitive (reversible) antagonists**
    Agonist + Competitive Antagonist
    - When we increase the amount of Antagonist
      - ✓ Decreases the full agonist response.
      - ✓ If increased too high: Block the response.
    - The concentration-effect curve is shifted down.
    - Decreasing efficacy (Emax).
    - Can be surmount by high concentrations of agonist.
    - Increases EC50 required for the same degree of response.
    - The concentration-effect curve is shifted to the right.
    - Thus, decreasing potency.

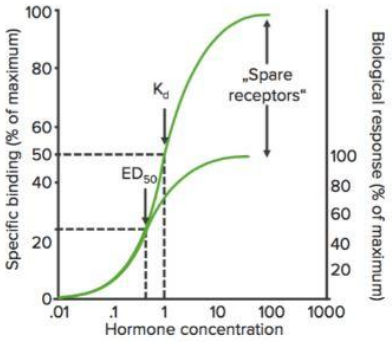


  - ➔ **Noncompetitive (irreversible) antagonists**
    - High amount = prevent the agonist response.
    - Cannot be overcome by any concentration of agonist.
      - ✓ Can be overcome only by replacement of the currently available receptors.
        - ⇨ Thus, their duration of action is relatively independent of its own rate of elimination and more dependent on the rate of turnover of receptor molecules.
      - ✓ Can be prevented from decreasing the Emax by **Spare receptors.**
    - The concentration-effect curve is shifted down.
    - Thus, decreasing the efficacy.



- Mechanisms of Drug Antagonism:
  - Interaction with receptor.
    - ➔ Reversible or irreversible.
  - Without Interaction with receptor.
    - ➔ Chemical antagonism: as protamine, counteract the effects of heparin by forming ionic bond.
      - Another example: Pralidoxime & dimercaprol.
  - Physiologic antagonism between regulatory pathways mediated by different receptors:
    - ➔ Glucocorticoid hormones and insulin.

- **Spare Receptors "Receptor Reserve".**
  - Receptors that synthesized by our cells more than normal.
  - Those that can elicit a maximal response at the same concentration of agonist that does not result in occupancy of all available receptors.
  - Mainly the heart (90% of β-Adrenoceptors are spare).



  - We can detect the presence of spare receptors by:

First. Emax vs Bmax:

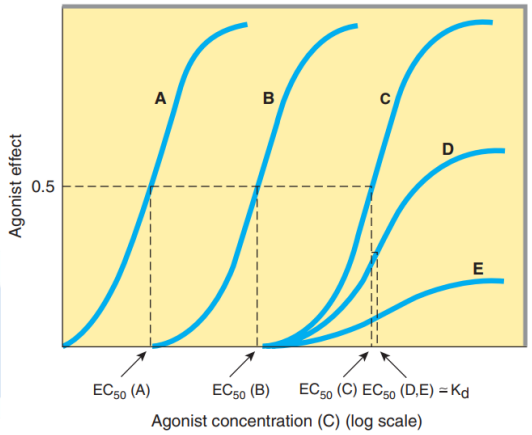
  - ➔ Spare receptors occur when:
    - Emax occurs at less than 100% binding.
      - ⇨ When EC50 is less than Kd.
    - Low EC50 & More Kd

⇨ Lower Emax = Rapid maximal response.
⇨ Higher Bmax = Higher number of receptors.

☒ Note:
- Kd: is the amount of drug needed to make 50% of the receptors occupied.
- EC50: is the amount of drug needed to make 50% of the maximum response.

☒ Which means that:
- If you have spare receptor:
  - ➔ A lower amount of drug is needed to make 50% of the full response.
  - ➔ A Higher amount of drug is needed to occupy 50% of the receptors.

Second. Adding of irreversible antagonist.

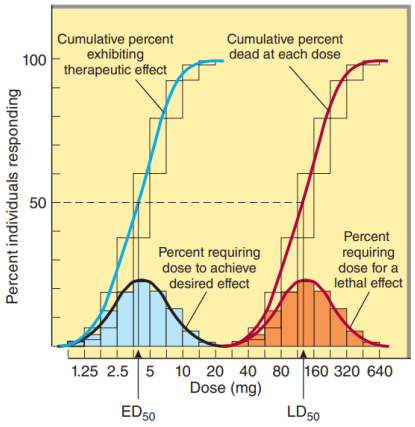


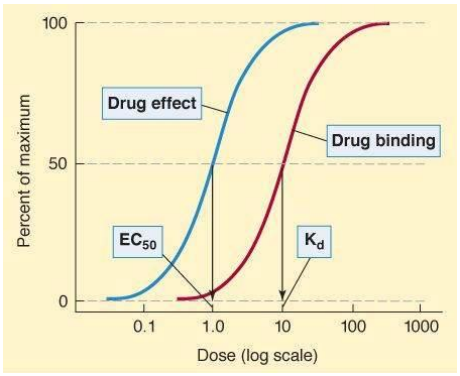
- ➔ Irreversible antagonists will block some receptors preventing agonist binding.
- ➔ At low doses = Blocking small number of receptors → Undiminished response.
- ➔ At higher doses = Blocking higher number of receptors → Undiminished response.
- ➔ At large doses = Blocking all spare receptors → Undiminished response.
- ➔ At larger doses = Blocking all spare receptors & some normal ones → diminished response.

- Types of spareness:
  - Receptors are spare in number relative to the number of downstream signaling mediators.
    - ➔ We have a cell with 4 receptors & 4 effectors:
      - If we give it an agonist equals to KD this will mean
        - ⇨ Two receptors will be occupied, and two effectors will be stimulated.
    - ➔ If we increase it to 40 receptors & 4 effectors
      - Lower concentration of agonist is sufficient to occupy 2 of the 40 receptors and this low concentration of agonist is able to elicit a half maximal response.
  - Temporal
    - ➔ After the receptor activation & downstream signaling mediators are activated.
    - ➔ Those activated mediators' lifetime may greatly outlast the Agonist receptor interaction.
    - ➔ Which means that:
      - We need a few receptors to be activated.
      - Because the mediators persist longer than the binding event itself.

Quantal dose-effect curve

Terminology:





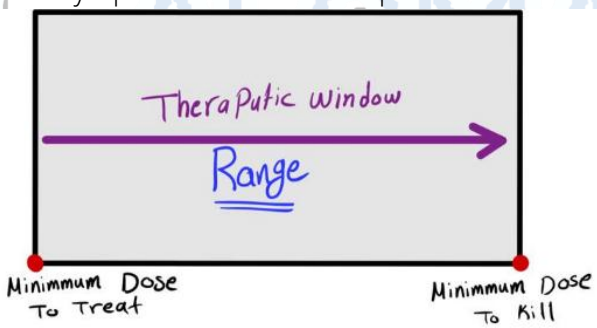
- ED50 (median effective dose): it is the dose at which 50% of individuals exhibit a certain effect.
- TD50 (median toxic dose): it is the dose that produces the toxic effect in 50% of animals.
- LD50 (median lethal dose): If the toxic effect is death of the animal.
- **Therapeutic index**:
  - The ratio between the drug dose to produce a desired effect to that produces undesired effect.
  - It measures the safety of a particular drug & estimates its potential benefits.
  - **Therapeutic index** $= \frac{\mathbf{TD50}}{\mathbf{ED50}}$.

	Drug A	Drug B
TD50	500mg	1000mg
ED50	50mg	20mg
Index	10	50

➔ Drug B:

- Safer than A, due to higher therapeutic index.

- Therapeutic window:
  - The range between minimum toxic dose & minimum therapeutic dose.
    - ➔ Drugs of headache (Paracetamol): large Therapeutic window.
    - ➔ Drugs of Hodgkin's lymphoma: small Therapeutic window.



☒ **Therapeutic window depends critically on the severity of the disease being treated.**

➔ **The larger the window thus the safer of drug.**

☒ **The curve at first is (quantal dose-effect curve) where we can plot the above measurement.**

- It indicates the **variability** of responsiveness among individuals.
- Give us critical information for making rational therapeutic decisions.

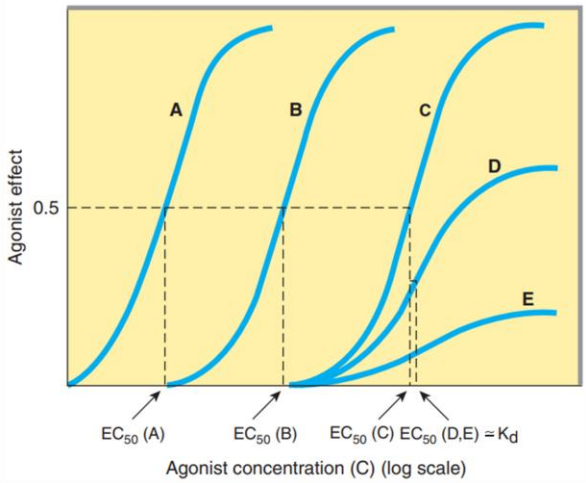
Additions:

- Practical efficacy:

- A drug's efficacy for achieving a therapeutic effect may be **limited by** the drug's propensity to cause a toxic.
- Thus, we must choose the drug that produces maximal benefit and minimal toxicity.

Question) Fill the blanks:

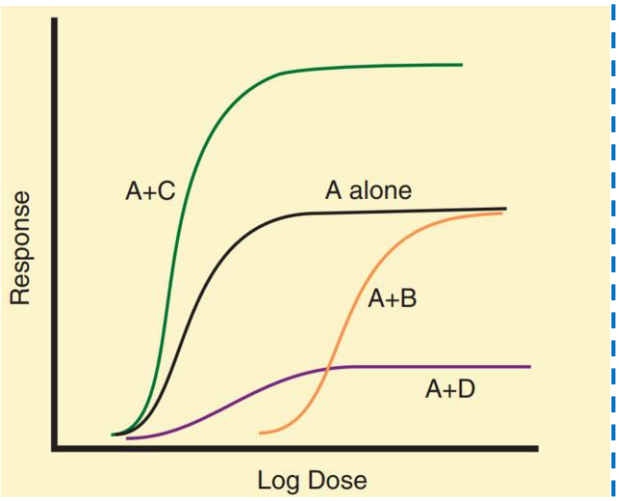
1. The more potent drug is _____.
2. The drug with least efficacy _____.
3. The drug with highest affinity _____.
   Hint: the same number of receptors.
4. The drug with highest affinity _____.
   Hint: Assume that EC50 = Kd.
5. A partial agonist drug _____.
6. A Full Agonist drug _____.
7. What is the concentration of drug that produce 50% of the maximal effect _____.

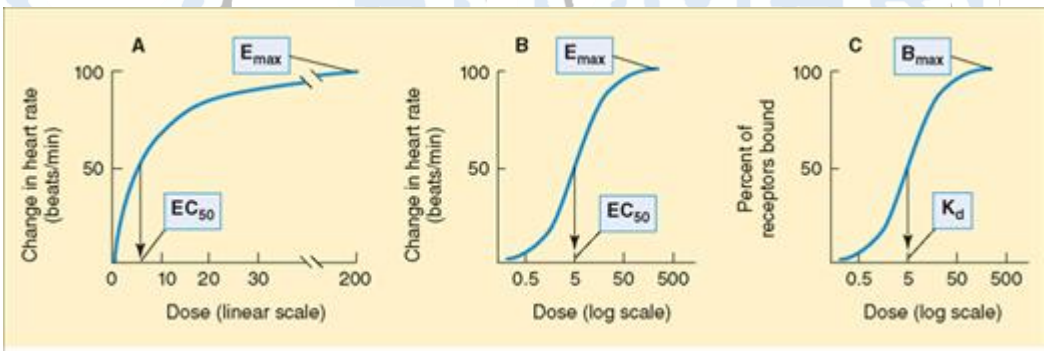


Question) Fill the blanks:

[redacted]

3. A & C represent a combination of _____ & _____.
4. Least effective combination is _____.
5. The curve that illustrates the combination that have higher affinity toward Ra* Formation is _____.





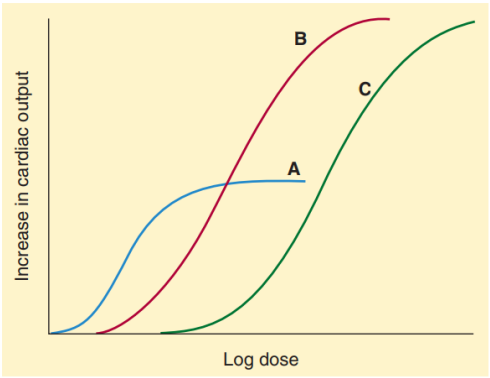
Q) Graphs B and C show Physiological effect vs concentration and Binding vs concentration for the same drug respectively. Comparing the two graphs, is it apparent that there are spare receptors?

Questions:

1. A 55-year-old woman with hypertension is to be treated with a thiazide diuretic. Thiazide A in a dose of 5 mg produces the same decrease in blood pressure as 500 mg of thiazide B. Which of the following statements best describes these results?
   (A) Thiazide A is more efficacious than thiazide B
   (B) Thiazide A is about 100 times more potent than thiazide B
   (C) Toxicity of thiazide A is less than that of thiazide B
   (D) Thiazide A has a wider therapeutic window than thiazide B
   (E) Thiazide A has a longer half-life than thiazide B

2. Graded and quantal dose-response curves are being used for evaluation of a new antiasthmatic drug in the animal laboratory and in clinical trials. Which of the following statements best describes graded dose-response curves?
   (A) More precisely quantitated than quantal dose-response curves
   (B) Obtainable from isolated tissue preparations but not from the study of intact subjects
   (C) Used to determine the maximal efficacy of the drug
   (D) Used to determine the therapeutic index of the drug
   (E) Used to determine the variation in sensitivity of subjects to the drug

3. Prior to clinical trials in patients with heart failure, an animal study was carried out to compare two new positive inotropic drugs (A and B) to a current standard agent (C). The results of cardiac output measurements are shown in the graph. Which of the following statements is correct?



   (A) Drug A is most effective
   (B) Drug B is least potent
   (C) Drug C is most potent
   (D) Drug B is more potent than drug C and more effective than drug A
   (E) Drug A is more potent than drug B and more effective than drug C

4. A study was carried out in isolated intestinal smooth muscle preparations to determine the action of a new drug "novamine," which in separate studies bound to the same receptors as acetylcholine. In the absence of other drugs, acetylcholine caused contraction of the muscle. Novamine alone caused relaxation of the preparation. In the presence of a low concentration of novamine, the EC50 of acetylcholine was unchanged, but the Emax was reduced. In the presence of a high concentration of novamine, extremely high concentrations of acetylcholine had no effect. Which of the following expressions best describes novamine?
   (A) A chemical antagonist
   (B) An irreversible antagonist
   (C) A partial agonist
   (D) A physiologic antagonist
   (E) A spare receptor agonist

5. Beta adrenoceptors in the heart regulate cardiac rate and contractile strength. Several studies have indicated that in humans and experimental animals, about 90% of β adrenoceptors in the heart are spare receptors. Which of the following statements about spare receptors is most correct?
   (A) Spare receptors, in the absence of drug, are sequestered in the cytoplasm
   (B) Spare receptors may be detected by finding that the drug-receptor interaction lasts longer than the intracellular effect
   (C) Spare receptors influence the maximal efficacy of the drug-receptor system
   (D) Spare receptors activate the effector machinery of the cell without the need for a drug
   (E) Spare receptors may be detected by the finding that the EC50 is smaller than the Kd for the agonist

6. Two cholesterol-lowering drugs, X and Y, were studied in a large group of patients, and the percentages of the group showing a specific therapeutic effect (35% reduction in low-density lipoprotein [LDL] cholesterol) were determined. The results are shown in the following table.

Drug Dose (mg)	Percent Responding to Drug X	Percent Responding to Drug Y
5	1	10
10	5	20
20	10	50
50	50	70
100	70	90
200	90	100

   Which of the following statements about these results is correct?
   (A) Drug X is safer than drug Y
   (B) Drug Y is more effective than drug X
   (C) The 2 drugs act on the same receptors
   (D) Drug X is less potent than drug Y
   (E) The therapeutic index of drug Y is 10

7. Sugammadex is a new drug that reverses the action of rocuronium and certain other skeletal muscle-relaxing agents (nondepolarizing neuromuscular blocking agents). It appears to interact directly with the rocuronium molecule and not at all with the rocuronium receptor. Which of the following terms best describes sugammadex?
   (A) Chemical antagonist
   (B) Noncompetitive antagonist
   (C) Partial agonist
   (D) Pharmacologic antagonist
   (E) Physiologic antagonist

THE END OF CHAPTER 2-1