PHARMACOLOGY

Pharmacodynamics

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DISCLOSURE

None

Use Statement

LEARNING OBJECTIVES

1. Define receptors and receptor coupling.
2. Describe how receptors can be classified.
3. Describe how receptors can be regulated.
4. Explain receptor occupancy theory and its relationship to the maximum effect a drug can produce.
5. Define and graphically represent agonist, full agonist, partial agonist, inverse agonist, and antagonist.
6. Interpret dose-response curves that illustrate affinity, efficacy, and potency of different drugs.
7. Describe and graphically represent changes to agonist potency and efficacy in the presence of competitive antagonists, noncompetitive antagonists, and partial agonists.
8. Describe and graphically represent alterations in dose-response relationships resulting in increased or decreased response (tolerance, tachyphylaxis, resistance, additive, synergism, potentiation).
9. Calculate therapeutic index, toxic dose, and effective dose when given sufficient information.

PHARMACODYNAMICS

Study of biochemical and physiological effects of a drug and their mechanism of action (MOA) at the organ system/subcellular/macro cellular levels

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INTRODUCTION TO RECEPTOR THEORY

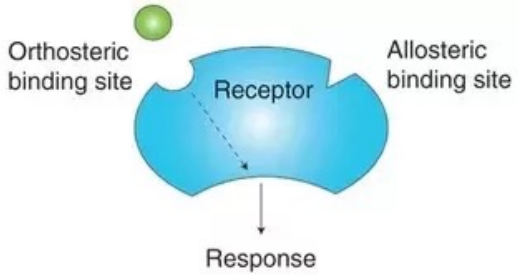
Pharmacodynamics

PHARMACODYNAMICS & RECEPTORS

Therapeutic and toxic effects of drugs result from interactions with molecules in patients

Most drugs act by associating with specific macromolecules that alter the macromolecule's biochemical or biophysical activities

Receptor is 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



PHARMACODYNAMICS & RECEPTORS

1. Receptors largely determine quantitative relations between drug dose or concentration and pharmacologic effects.
2. Receptors are responsible for selectivity of drug action.
3. Receptors mediate the actions of pharmacologic agonists and antagonists.

MOST DRUG RECEPTORS ARE PROTEINS

Many classes

- Regulatory proteins - mediate actions of endogenous chemical signals (eg, neurotransmitters, hormones)
- Enzymes (eg, HMG-CoA reductase)
- Transport proteins (eg, Na+/K+ ATPase)
- Structural proteins (eg, tubulin)

RECEPTOR OCCUPANCY THEORY

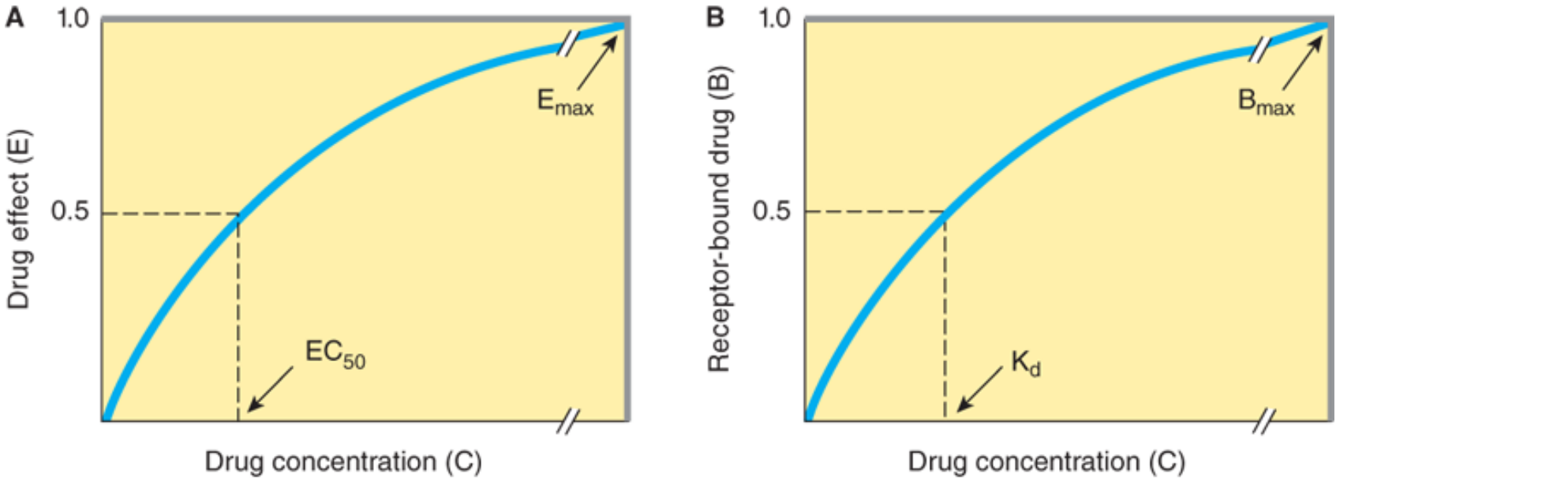
$$D + R \leftrightarrows D\text{–}R \ complex \Rightarrow EFFECT$$

Response occurs from a receptor when a drug binds it

The more receptors that are bound by drug, the greater the response

When all receptors are bound, the maximum response is achieved

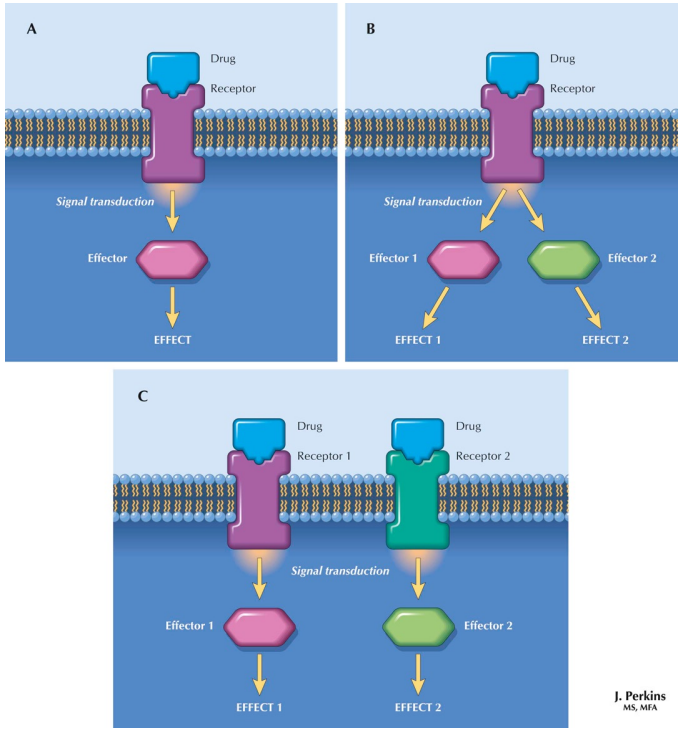
DRUG EFFECT AND RECEPTOR-BOUND DRUG



E is effect observed at concentration C
Emax is the maximal response that can be produced by a drug
EC50 is the concentration of drug that produces 50% maximal effect

B relates to the concentration of free drug C
Bmax is the total concentration of receptor sites
Kd is the equilibrium dissociation constant (C of free drug at which half-maximal binding is observed)

RECEPTOR COUPLING

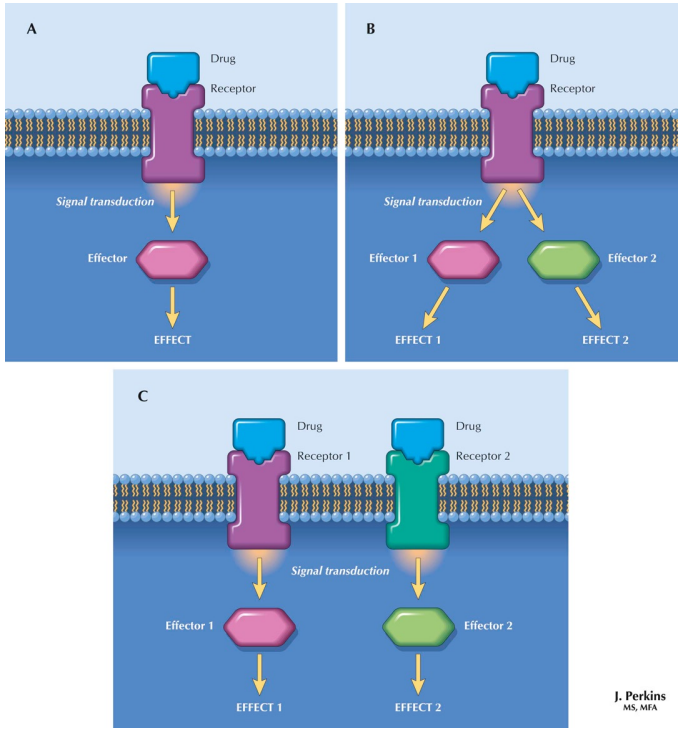


In most cases, a drug activates or inhibits only one molecule in a long series of biochemical reactions

When a drug binds to a receptor on a cell membrane, the extracellular drug signal must be passed to the intracellular physiologic processes

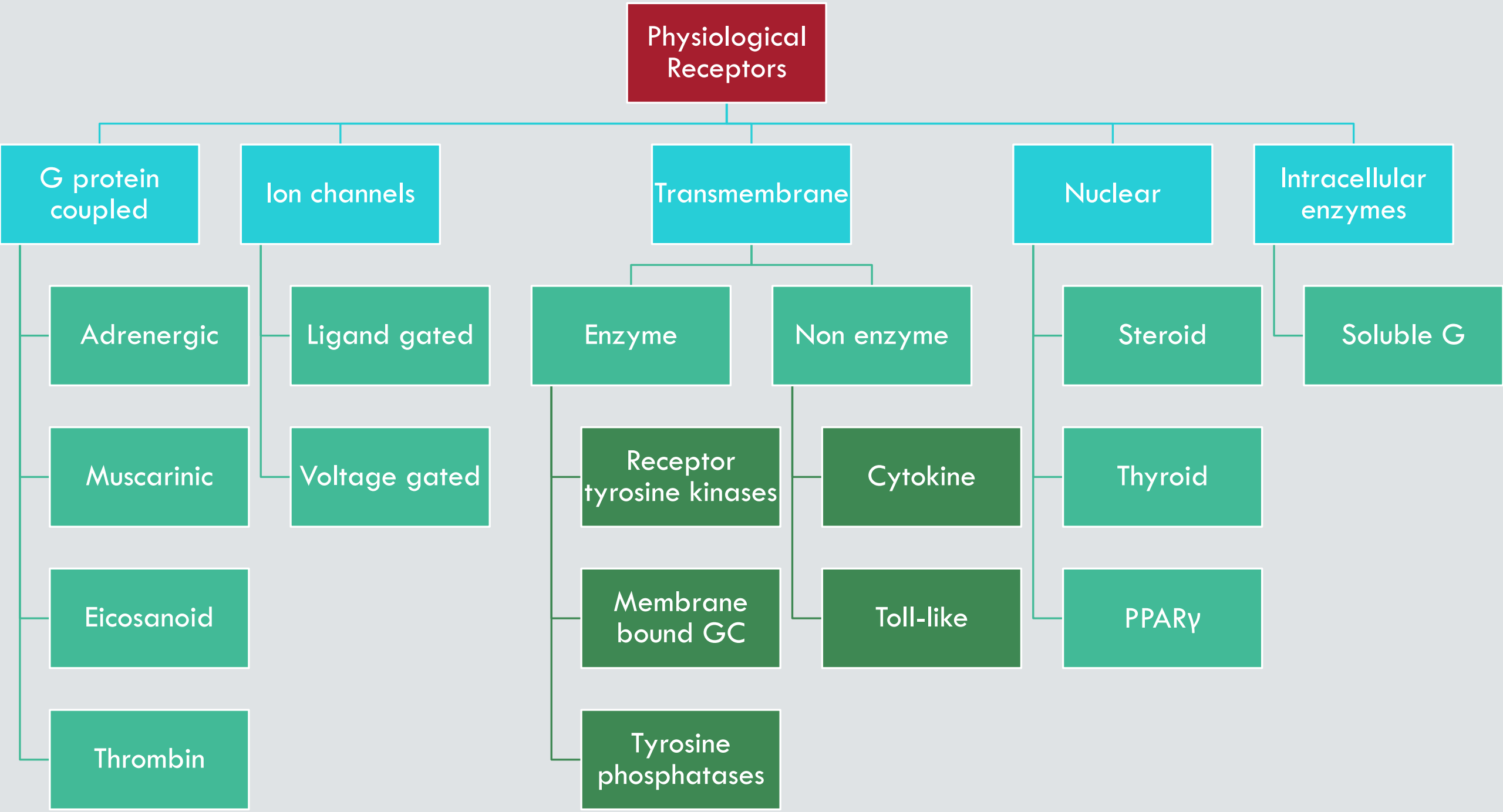
- Must be converted (transduced) to an intracellular message, the process termed **signal transduction**
- Effect of a drug depends on its receptors, the transduction pathways to which it is coupled, its level of receptor expression in cells, and its cellular response capacity

RECEPTOR COUPLING



A drug can

- Bind to one receptor coupled to one effector (transduction pathway) and produces one effect (A)
- Bind to one receptor coupled to more than one effector so it produces more than one effect in the same or different cells (B)
- Have affinity for more than one receptor, with each receptor coupled to a different effector (C)
  - Effect 2 can be a therapeutic end point or an adverse effect


Physiological Receptors
G protein coupled
Ion channels
Transmembrane
Nuclear
Intracellular enzymes
Adrenergic
Muscarinic
Eicosanoid
Thrombin
Ligand gated
Voltage gated
Enzyme
Non enzyme
Receptor tyrosine kinases
Membrane bound GC
Tyrosine phosphatases
Cytokine
Toll-like
Steroid
Thyroid
PPARγ
Soluble G

CATEGORIES OF DRUGS THAT INTERACT WITH RECEPTORS

AGONIST

- Drug that binds to physiological receptor that mimics the regulator effects of the endogenous signaling compounds

PRIMARY AGONIST

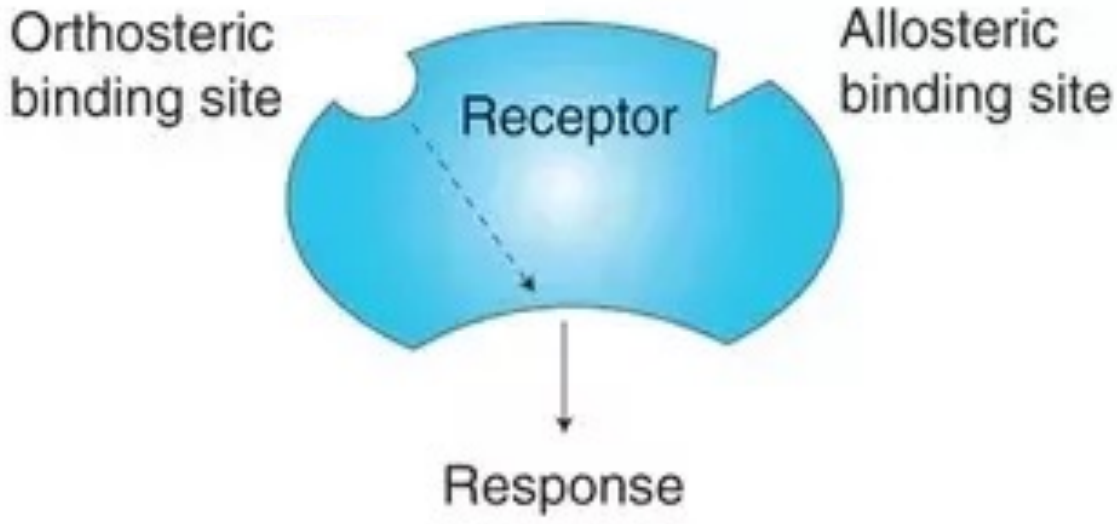
- Agonist that binds to the same recognition site as the endogenous agonist (orthosteric site)

ALLOSTERIC (OR ALLOTOPIC) AGONIST

- Agonist that binds to a different region (allosteric or allotopic site) on the receptors

ACTIVE LEARNING

Using the provided receptor, draw where a primary agonist would bind. Now draw where an allotropic agonist would bind.



ANTAGONISTS, PARTIAL, & INVERSE AGONISTS

ANTAGONIST

- Drugs that block or reduce action of an agonist (binding of an antagonist to a receptor does NOT produce a biological effect)
- Can compete with agonist for the same or overlapping site on the receptor (syntopic interactions) OR interact with other sites on the receptor (allosteric antagonism)

PARTIAL AGONIST

- Drugs that are only partially as effective as agonists

INVERSE AGONISTS

- Many receptors exhibit constitutive activity in the absence of a regulatory ligand
- Drugs that stabilize such receptors in an inactive conformation are inverse agonists

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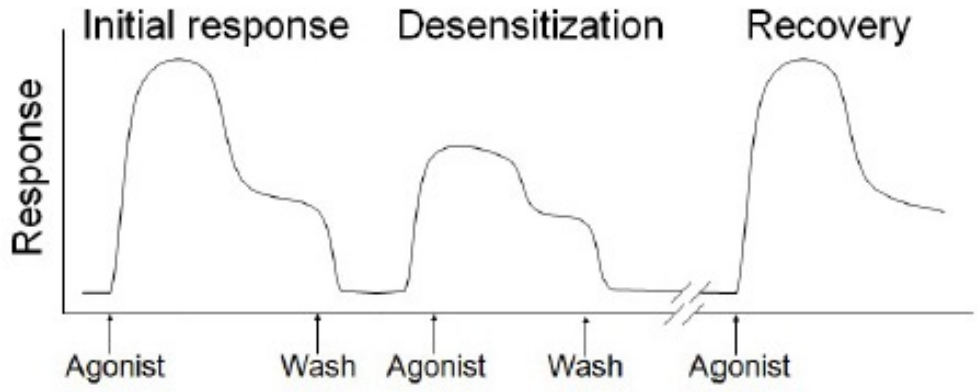
RECEPTOR REGULATION

DESENSITIZATION

Receptors subject to regulatory and homeostatic control

Continued stimulation → desensitization (down regulation of receptor number)

- Effect that follows continued or subsequent exposure to the same agonist is diminished
- May result through down-regulation of receptors in the membrane
  - Fewer receptors → ↓ response

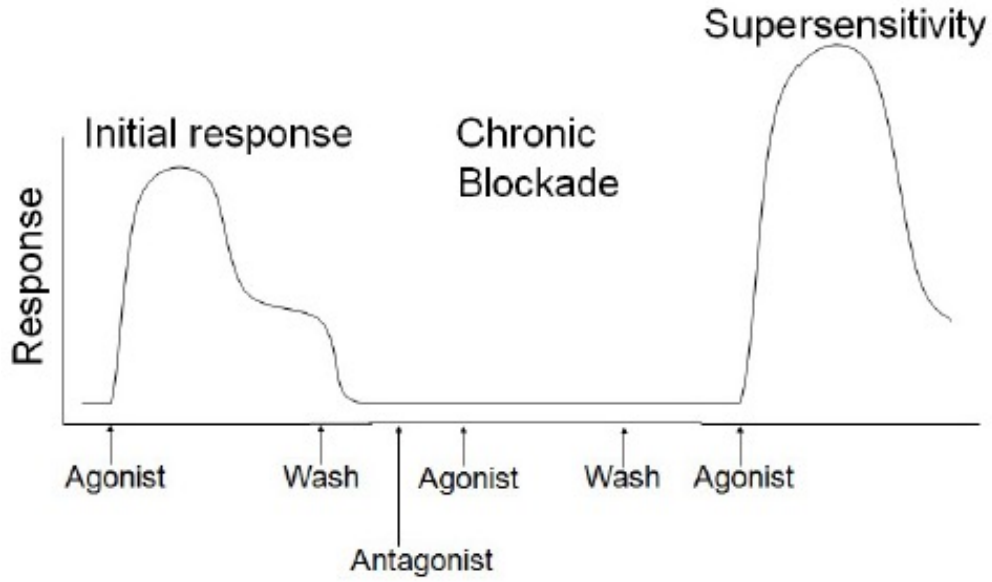


SUPERSENSITIVITY

Supersensitivity to agonists frequently follow chronic reduction in receptor stimulation

Chronic inhibition → upregulation or ↑ in receptor number

When inhibitor is removed, there are more receptors available to interact with drug and response is enhanced



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EFFICACY & POTENCY

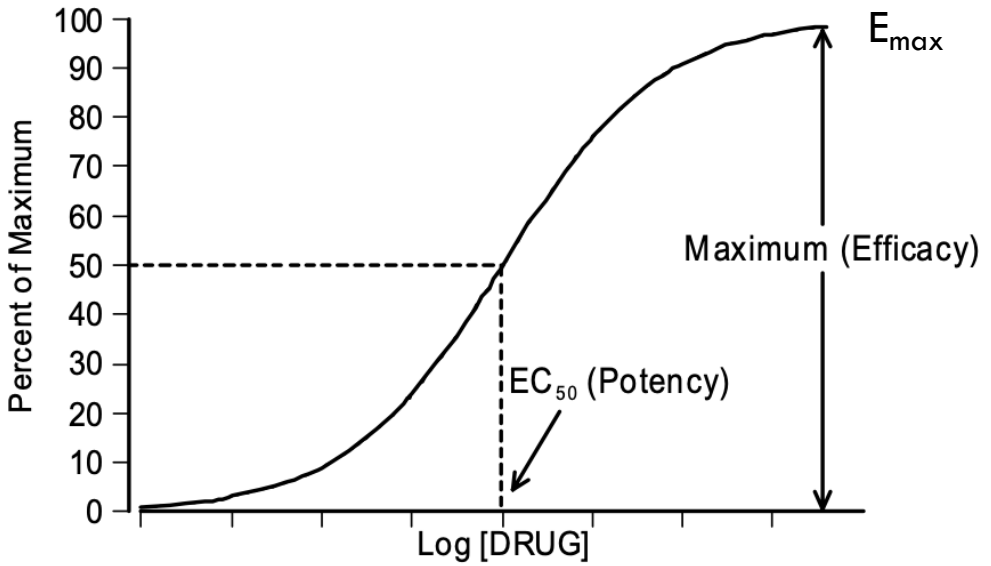
Pharmacodynamics

TYPICAL DOSE-RESPONSE RELATIONSHIP

Formation of drug-receptor complex → biological response

Magnitude of response is proportional to the number of drug-receptor complexes

Relationship between the drug concentration and the biological response shown as dose-response curve



EFFICACY & POTENCY

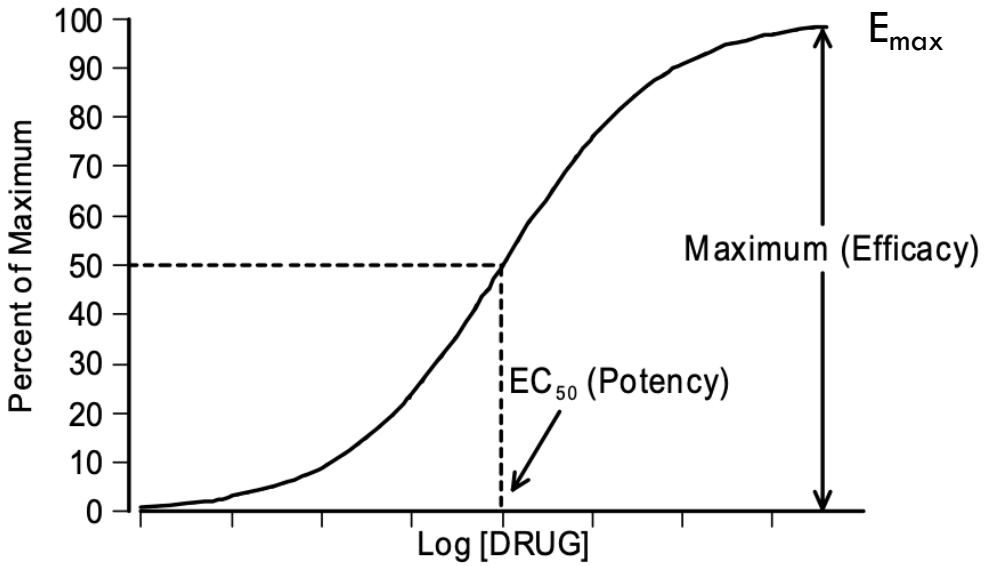
Most dose-response curves are plotted with the log of the concentration on the X-axis

Reaches max asymptote value when drug occupies ALL receptor sites

- Max measures drug's **efficacy** (Emax)

EC50 or ED50 is concentration or dose that causes half the max response

- EC50 or ED50 measures drug's **potency**



ACTIVE LEARNING

	Efficacy	Potency
Definition		
Expression		

ACTIVE LEARNING

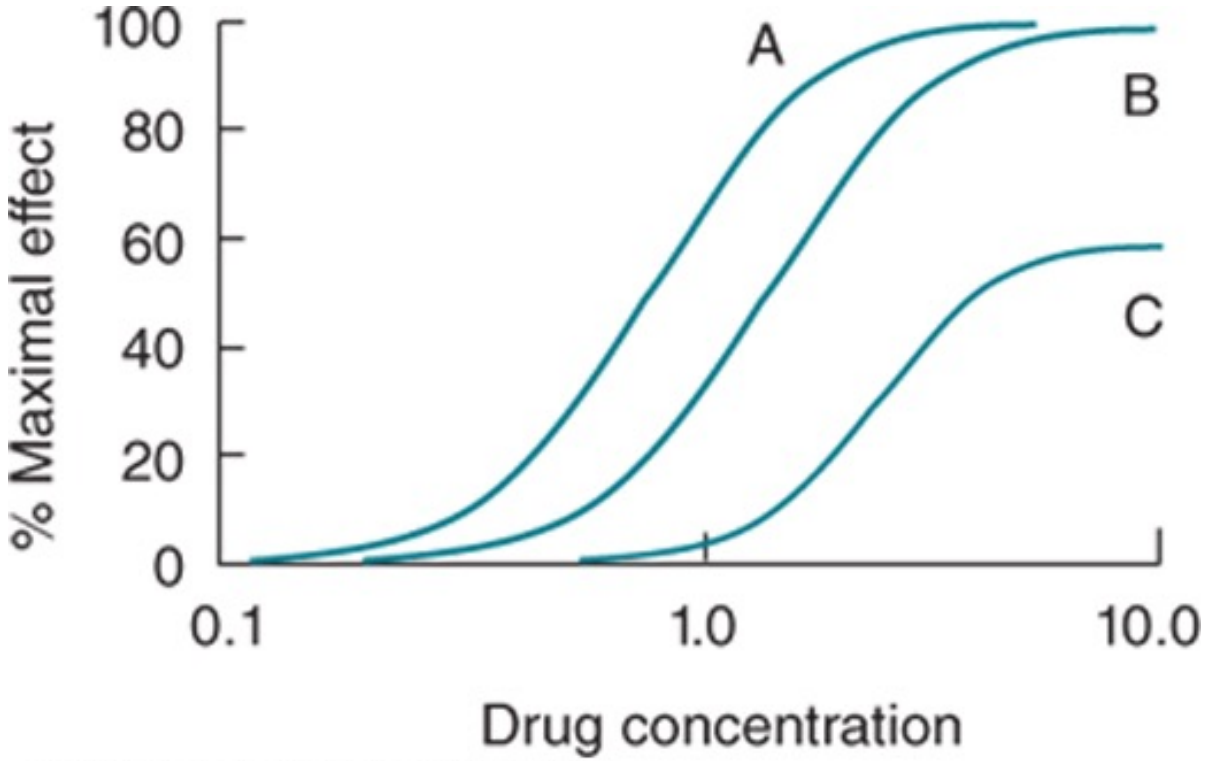
Consider Drugs A, B, and C. They are each plotted on the following dose-response curve. Which drug(s) is/are the:

a. Most efficacious?

b. Least efficacious?

c. Most potent?

d. Least potent?



Source: Janet L. Stringer: Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, Fifth Edition, www.accesspharmacy.com

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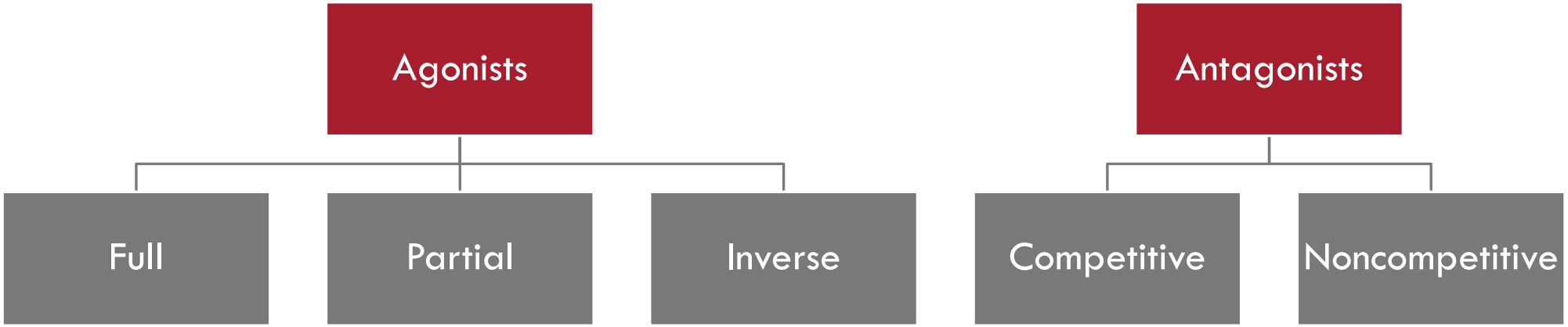
AGONISTS & ANTAGONISTS

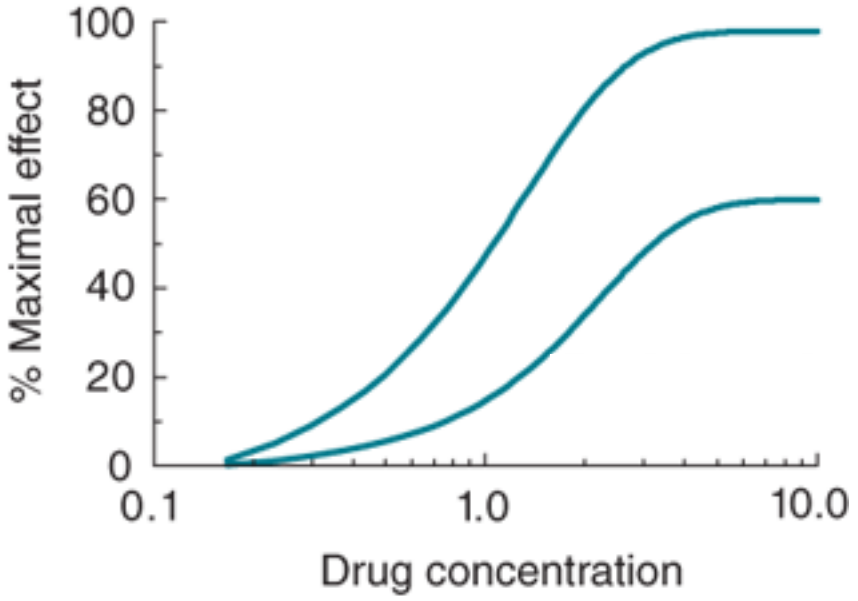
Pharmacodynamics



We will assume there are NO spare receptors in the system during this portion

ACTIVE LEARNING

Please label the dose-response curves with full agonist or partial agonist. Defend your answer.

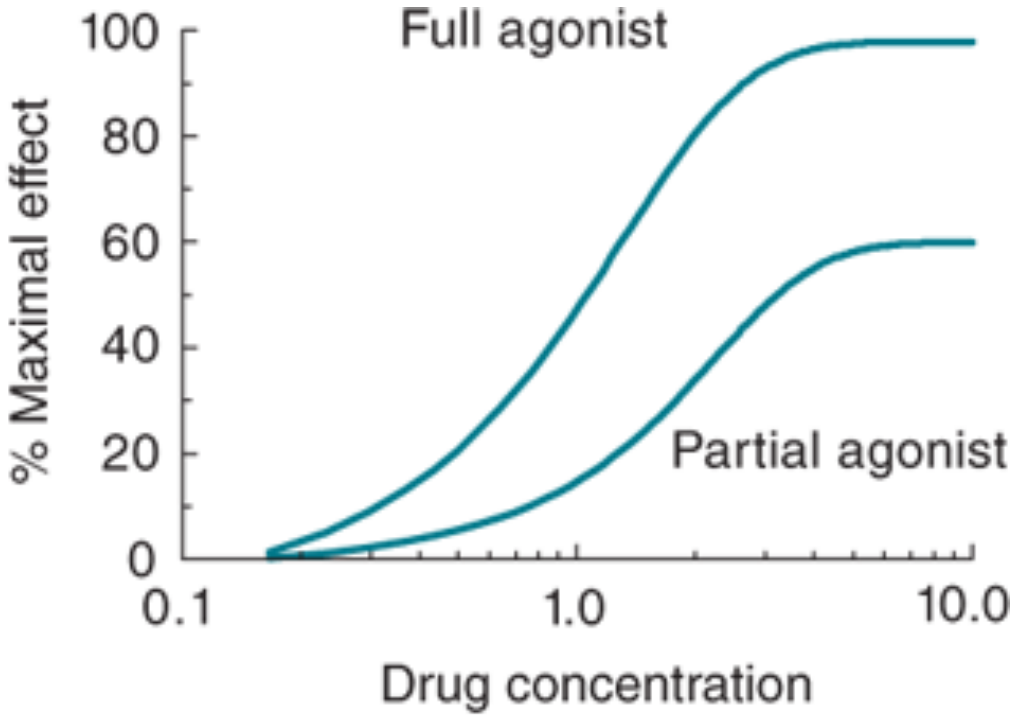


FULL AGONISTS & PARTIAL AGONISTS

Full agonists are capable of producing max response/effect when all receptors occupied

Partial agonists do NOT produce full response when all receptors occupied

- Partial agonist produces biological response, but cannot produce 100% of the biological response even at very high doses
- Partial agonists have lower efficacy



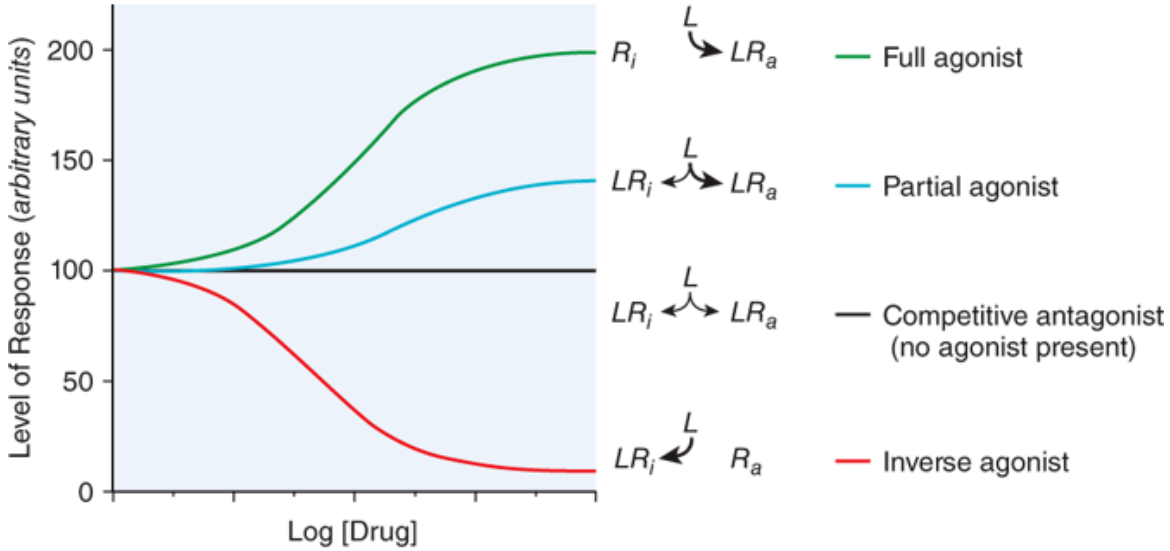
INVERSE AGONIST

Have opposite effects from full agonists

- Not the same as antagonists, which block the effects of both agonists and inverse agonists

For there to be inverse agonist in a receptor system, there must be activity in the basal, resting state in the absence of any ligand

- Net physiological result of an inverse agonist and an antagonist may be the same, the molecular mechanism is not
- Antagonists bind to the receptor, but they have no effect on the basal state
- Antagonists block the effects of both the agonists and inverse agonists



ANTAGONISTS

Drugs that bind to receptors without causing an effect; their binding **blocks** the binding of endogenous agonists

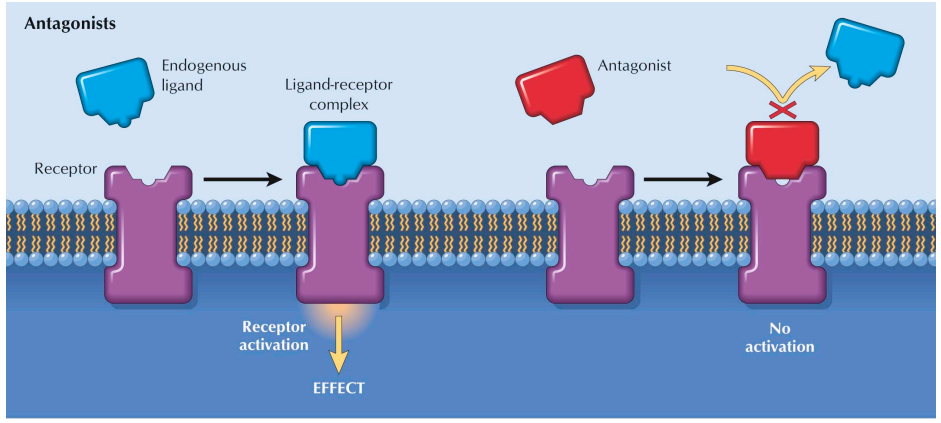
Possess affinity but not intrinsic activity (no effect on their own)

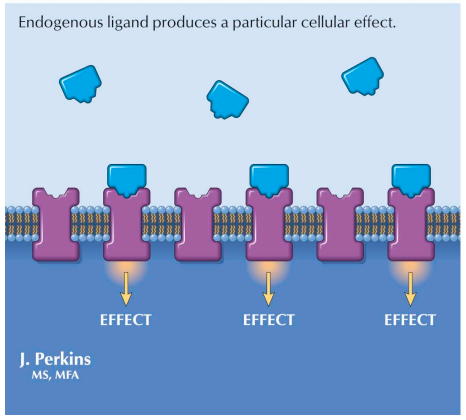
Binding of an antagonist to a receptor does NOT produce a biological effect

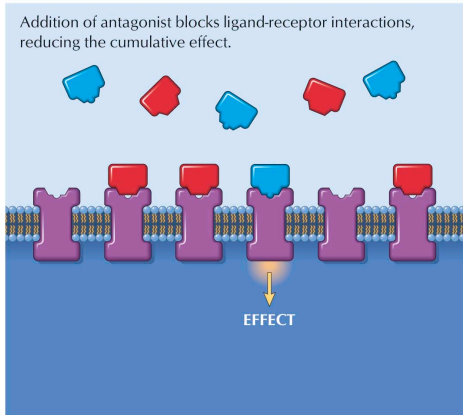
Types

- Competitive
- Noncompetitive
- Physiologic or functional

ANTAGONISTS







COMPETITIVE ANTAGONIST

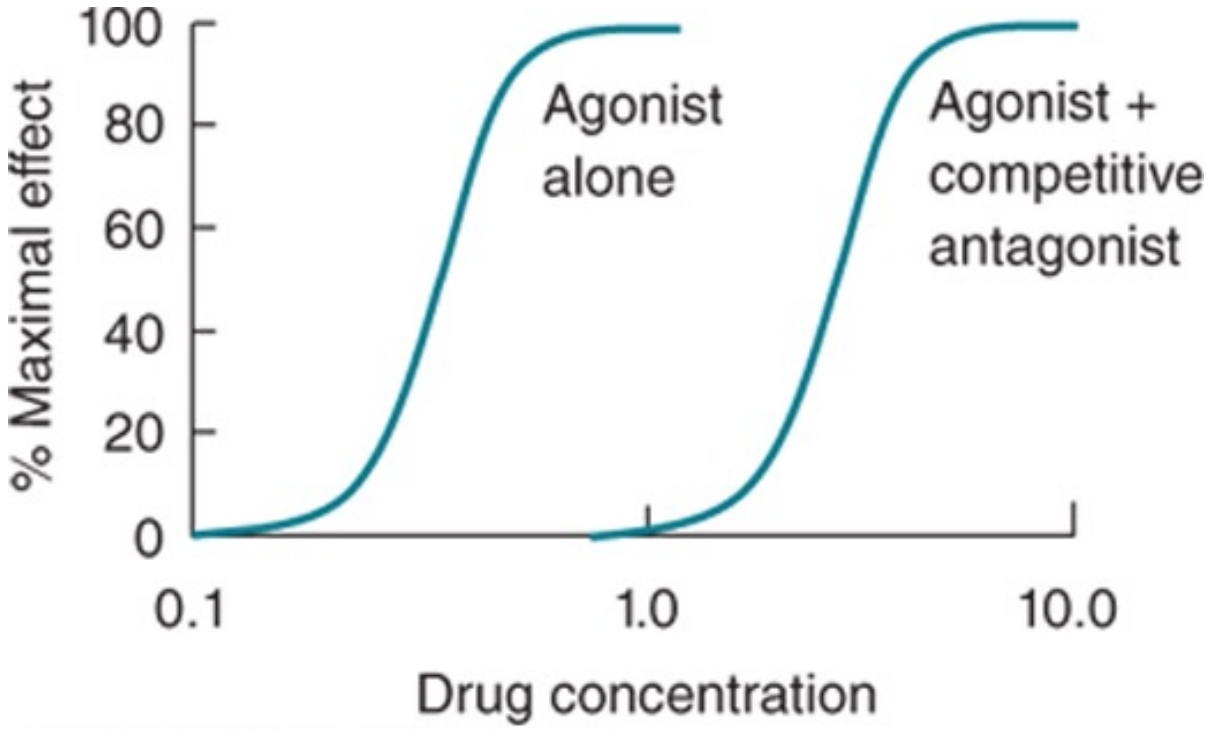
Competitive antagonists make the agonist look less potent → dose-response curve to the right

Compete for the **SAME** binding site on the receptor that agonist wants

- If agonist wins → response produced
- If antagonist wins → no response is produced

As agonist concentration ↑, odds that an agonist molecule will win the receptor spot and produce an effect ↑

- At high enough agonist concentration, the antagonist doesn't have a chance at the receptor (outnumbered)
- Effects are **SURMOUNTABLE**



Source: Janet L. Stringer: Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, Fifth Edition, www.accesspharmacy.com

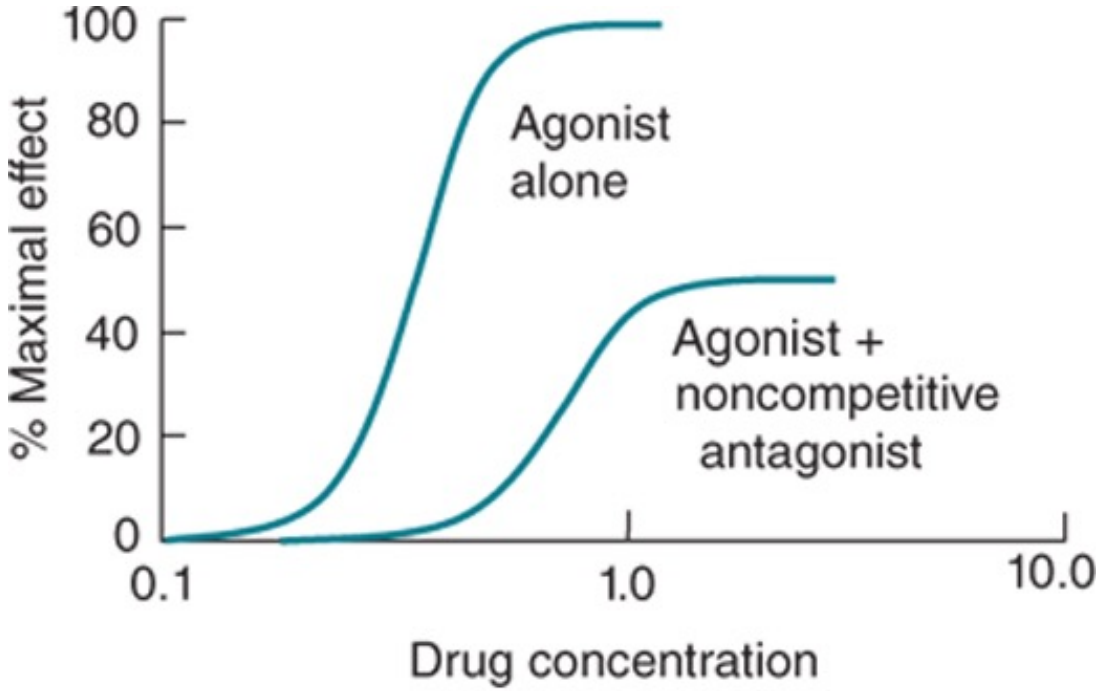
ORTHOSTERIC NONCOMPETITIVE ANTAGONIST

Noncompetitive (or uncompetitive) antagonists reduce the maximal effect

- Can **irreversibly** bind to the receptor so that agonist cannot be competed off

As agonist concentration increases, max response is NOT reached

- Effects are **NOT surmountable**



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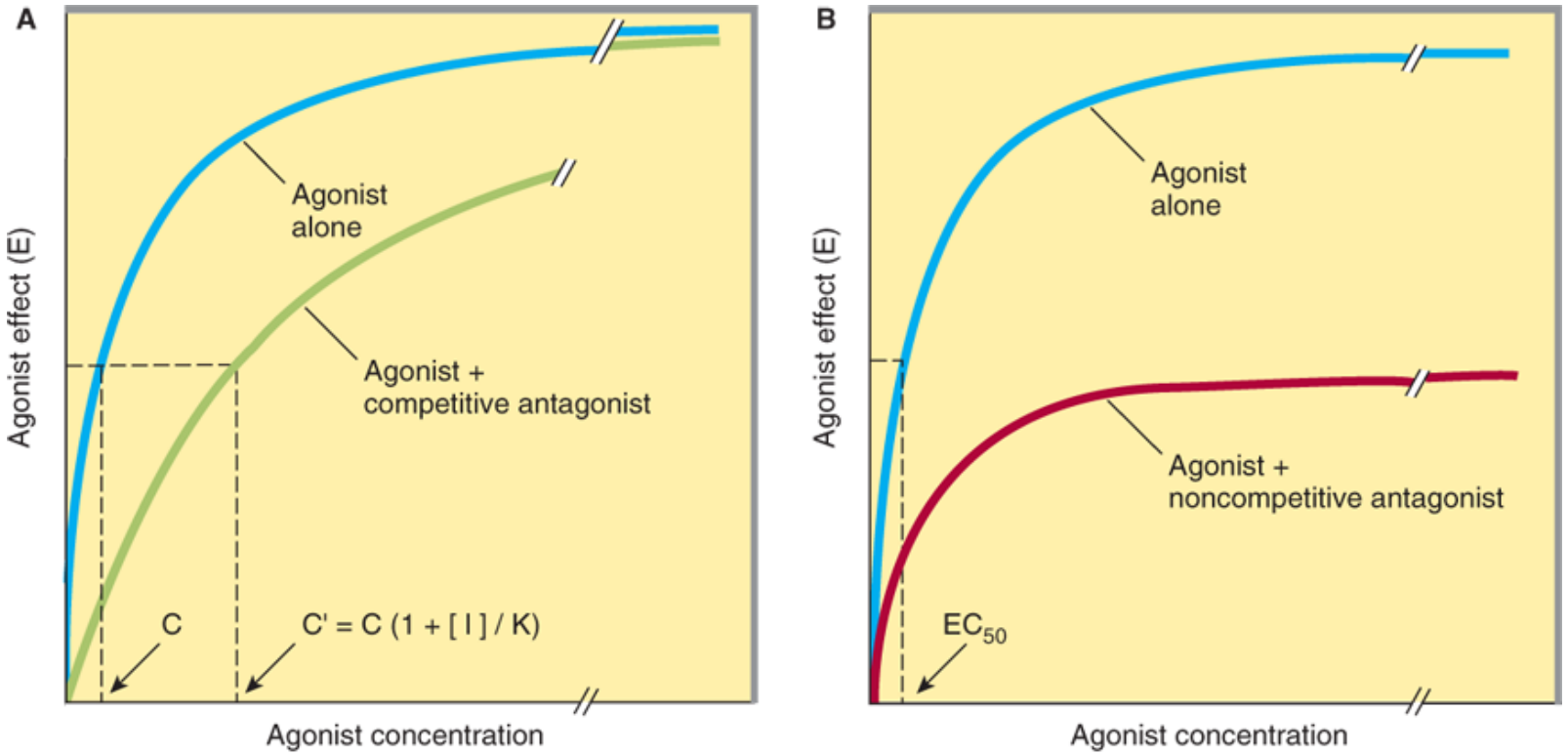
COMPETITIVE & NONCOMPETITIVE ANTAGONIST



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition

ACTIVE LEARNING

In which situations would a competitive antagonist be advantageous? In which situations would a noncompetitive antagonist be advantageous?

OTHER MECHANISMS OF DRUG ANTAGONISM

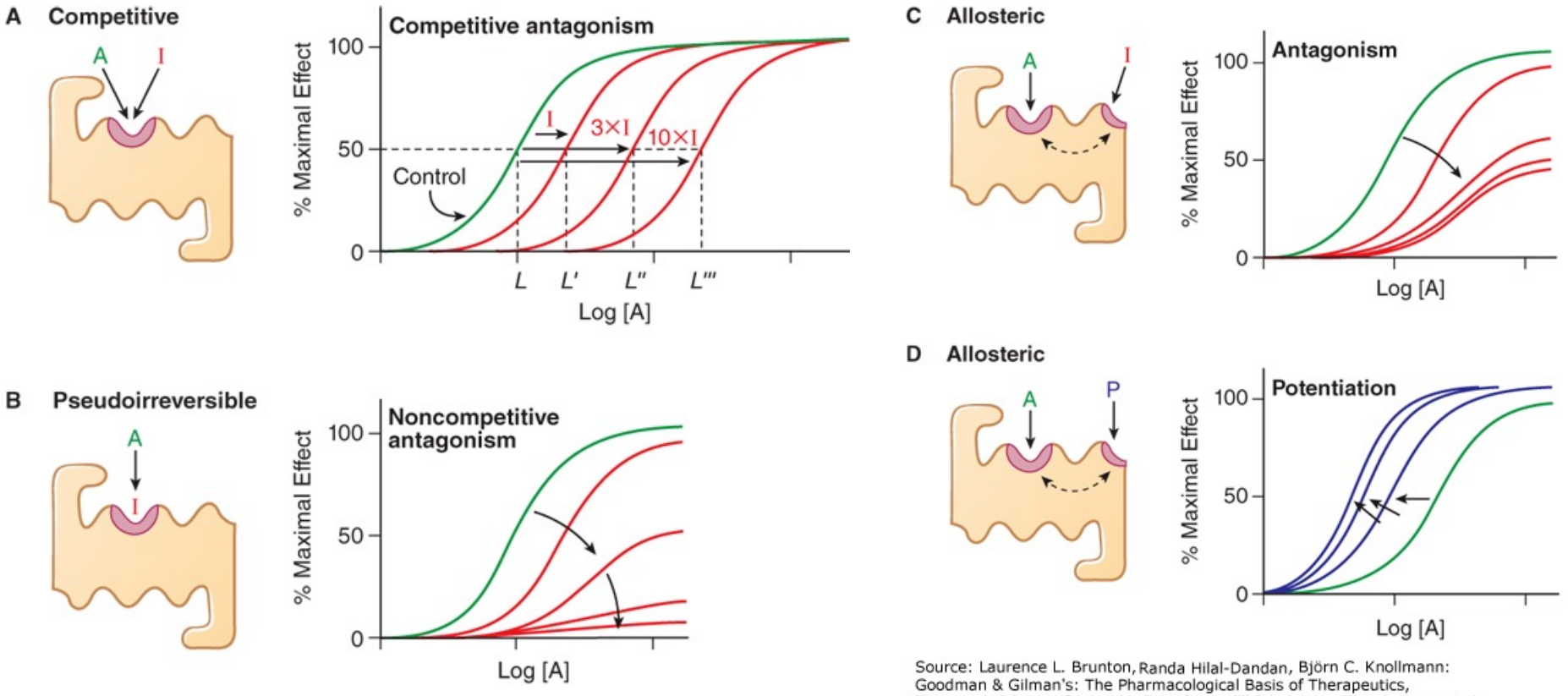
Antagonism can occur outside of drug-receptor interactions

Chemical antagonism

- Protamine (positively charged) counteracts heparin (negatively charged) – ionic binding makes the drug unavailable for physiologic effect

Physiologic antagonism

- Uses endogenous regulatory pathways mediated by different receptors
- Corticosteroids (nuclear steroid receptor) increase plasma glucose; insulin (tyrosine kinase receptor) can be used to lower plasma glucose



INTERACTIVE LEARNING

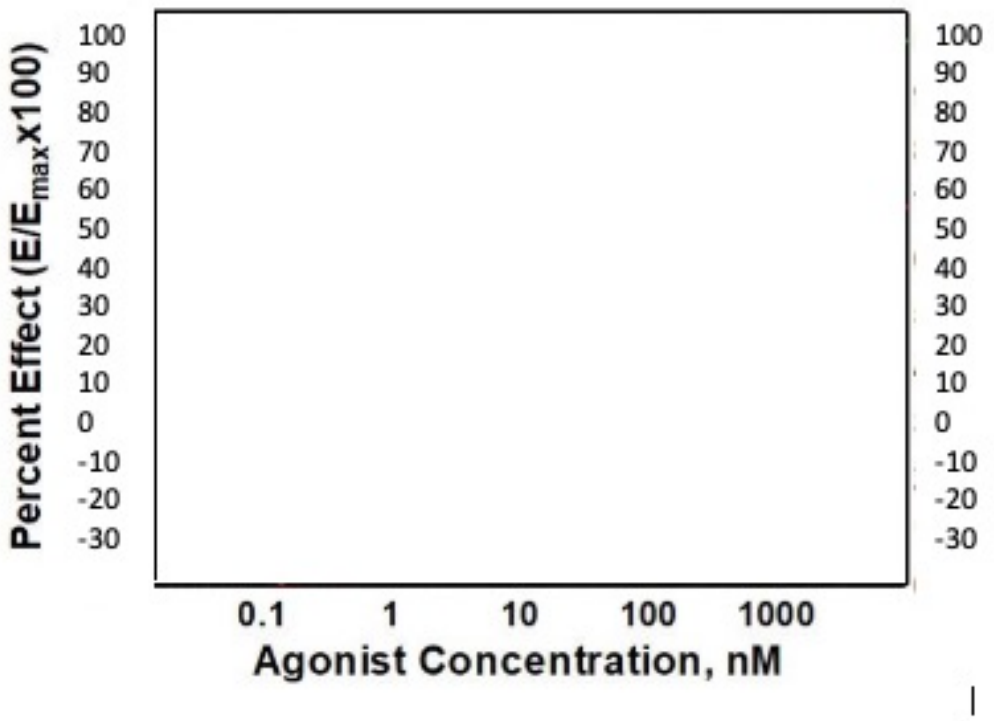
1. *4. Plot the following dose-responses on the provided chart.*

   Agonist alone

   Agonist + competitive antagonist

   Agonist + noncompetitive antagonist

   Inverse agonist



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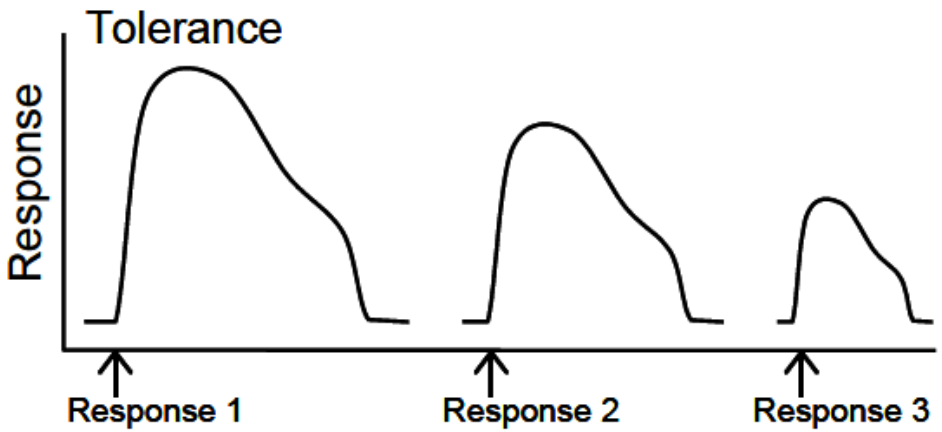
ALTERATIONS IN DOSE RESPONSE RELATIONSHIPS

TOLERANCE

Tolerance occurs when repeated exposure to a drug produces a diminished response to the drug

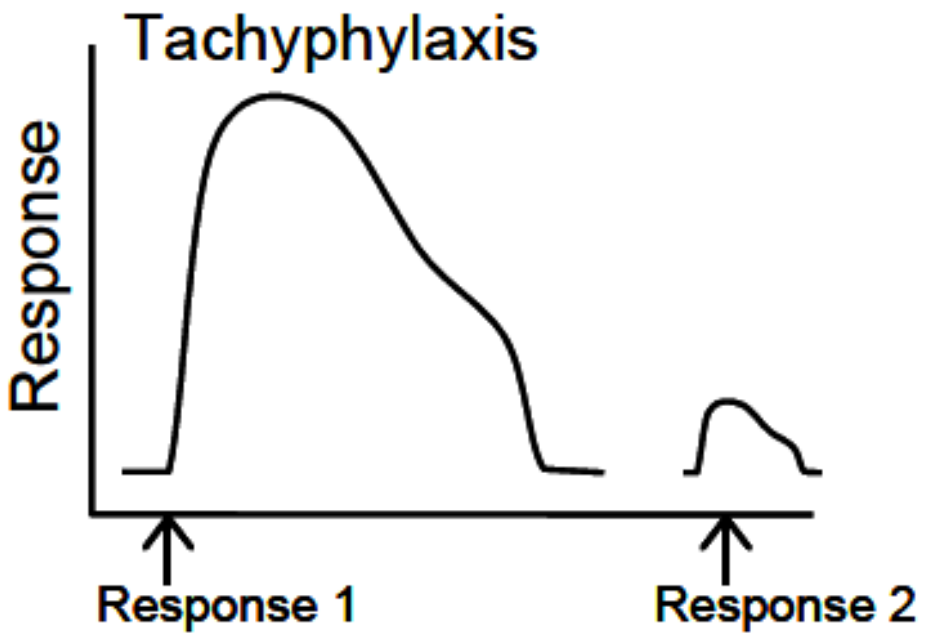
- May result from down-regulation of receptors



TACHYPHYLAXIS

Tachyphylaxis occurs when there is a rapid loss of response to a drug upon repeated administration

- May result from down-regulation of receptors

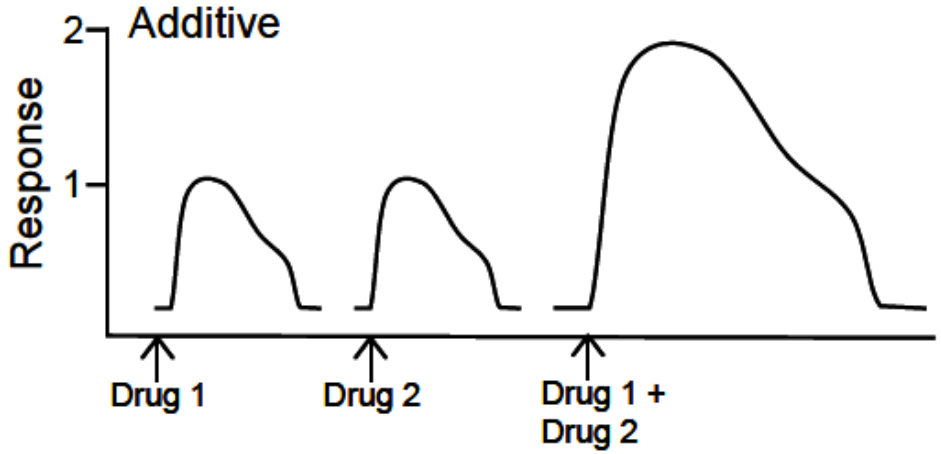


RESISTANCE

Diminished response to drugs used to inhibit cell growth or death

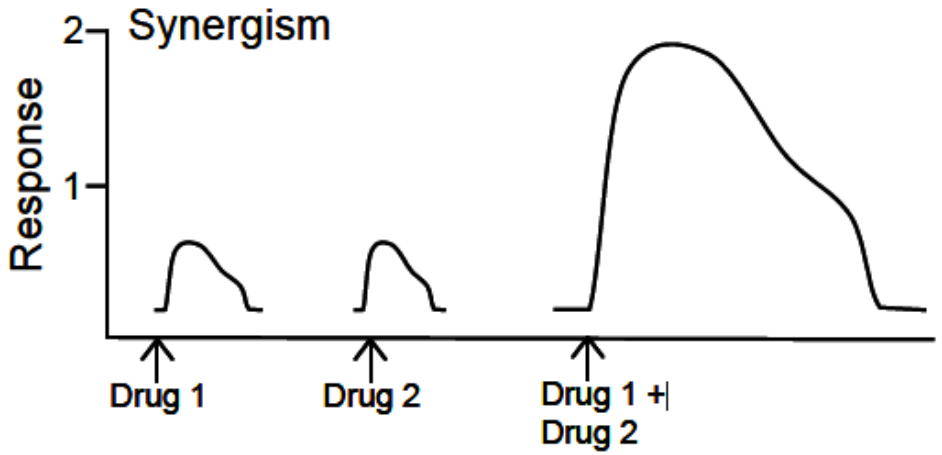
ADDITIVE

Additive response when two drugs given together produce an effect that is equal to the sum of their individual effects



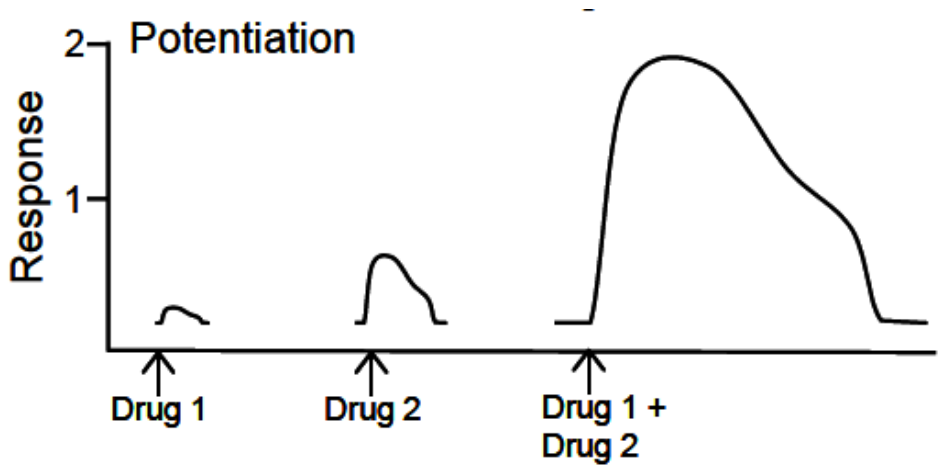
SYNERGISM

Synergism occurs when two drugs given together produce an effect that is greater than the sum of their individual effects



POTENTIATION

Potentiation occurs when administration of a drug with little or no effect enhances the effect of a second drug



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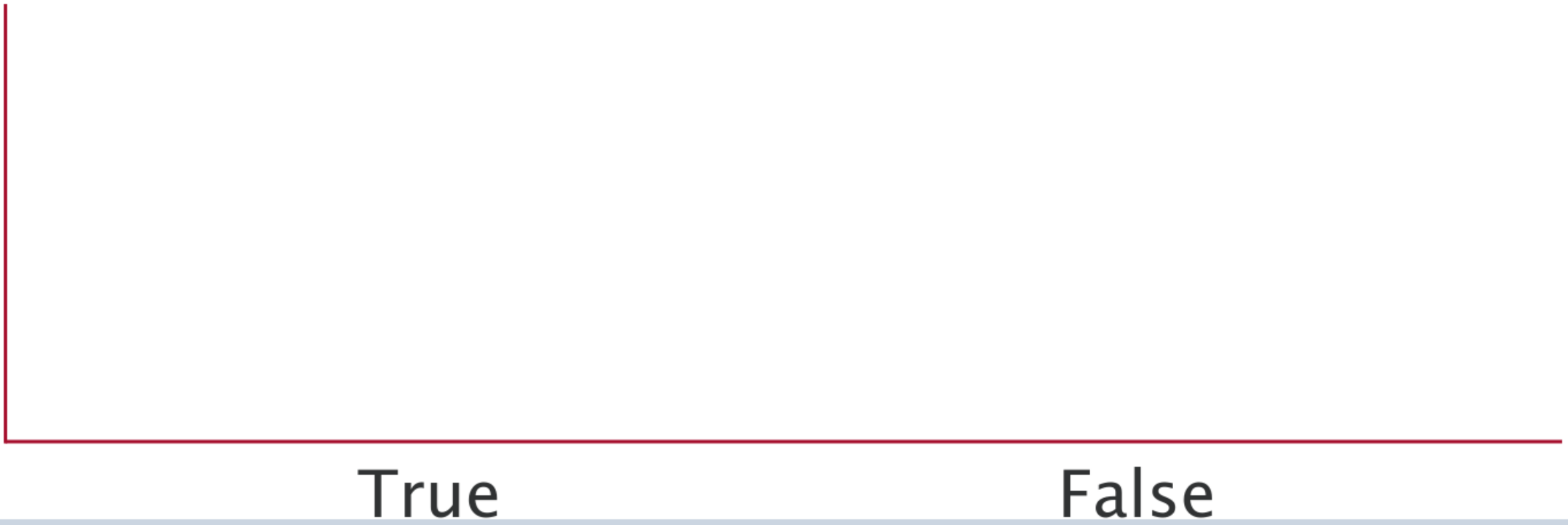
THERAPEUTIC INDEX

Pharmacodynamics

True or false: If the therapeutic index of penicillin (an antibiotic) is high, this means the toxic dose is much higher than the effective dose.



THERAPEUTIC INDEX

Measure of drug safety

- Drug with a higher therapeutic index is safer than one with a low therapeutic index
- Can use lethal dose or toxic dose
  - The toxic dose is the dose that is toxic to 50% of those that receive it
  - The lethal dose is the dose that is lethal to 50% of those that receive it

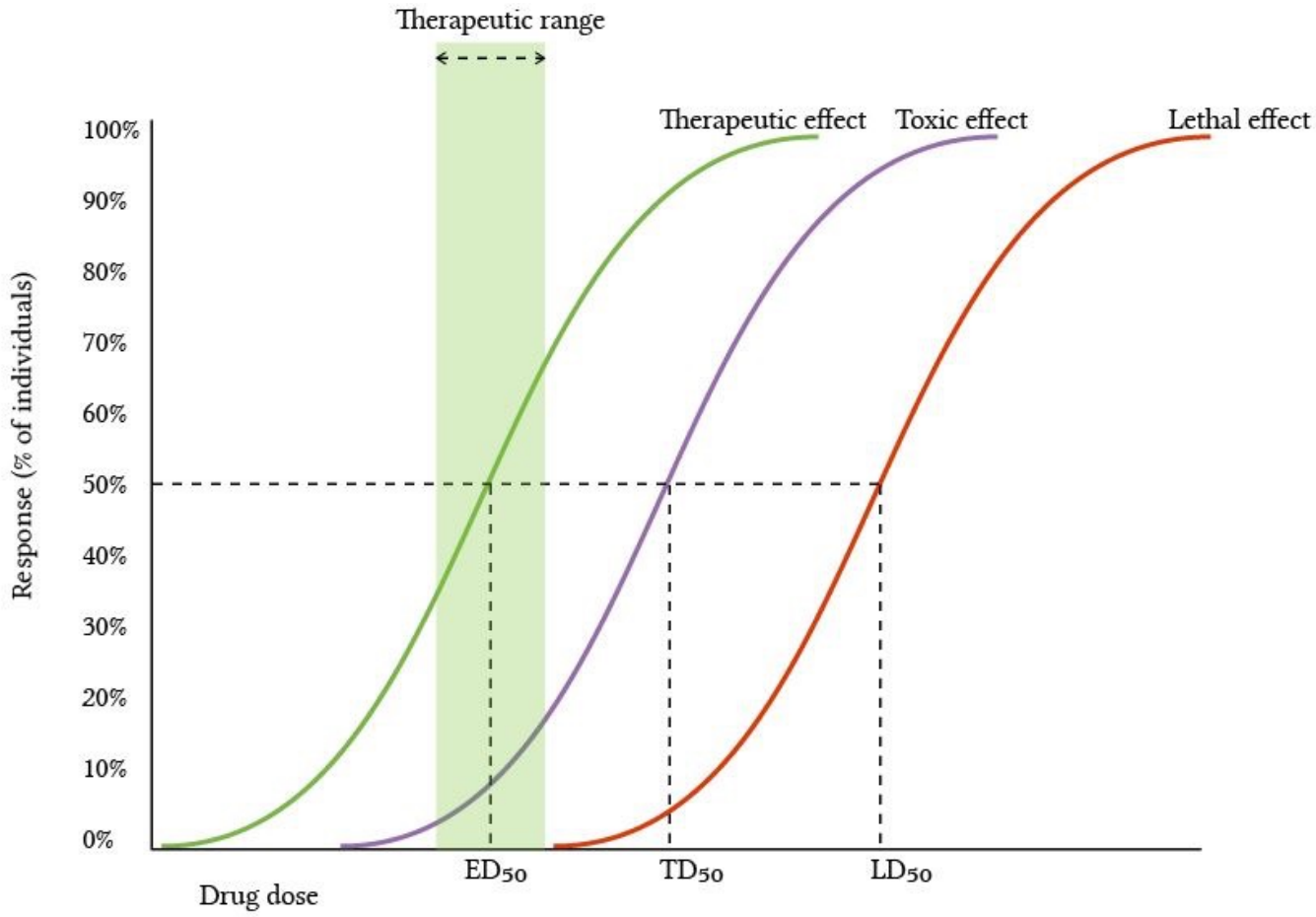
$$Therapeutic\ Index = \frac{median\ toxic\ dose}{median\ effective\ dose} = \frac{TD_{50}}{ED_{50}}$$

THERAPEUTIC INDEX

$$Therapeutic\ Index\ =$$

$$\frac{median\ toxic\ dose}{median\ effective\ dose}$$

$$= \frac{TD_{50}}{ED_{50}}$$



ACTIVE LEARNING

Consider an antibiotic that requires a median concentration of 2 mcg/mL for bactericidal effect, but causes toxicity at a median concentration of 25 mcg/mL. What is the therapeutic index of this antibiotic?

ACTIVE LEARNING

Consider an antibiotic that has a therapeutic index of 1.5 and requires a median concentration of 2 mcg/mL for bactericidal effect. What is the median toxic dose?

REFERENCE LIST

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ANY QUESTIONS?