Pharmacodynamics Part 1

Introduction to Drug-Receptor Interactions and the Dose-Response Relationship

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I am available to groups and individuals for pharmacology help and discussions by appointment.

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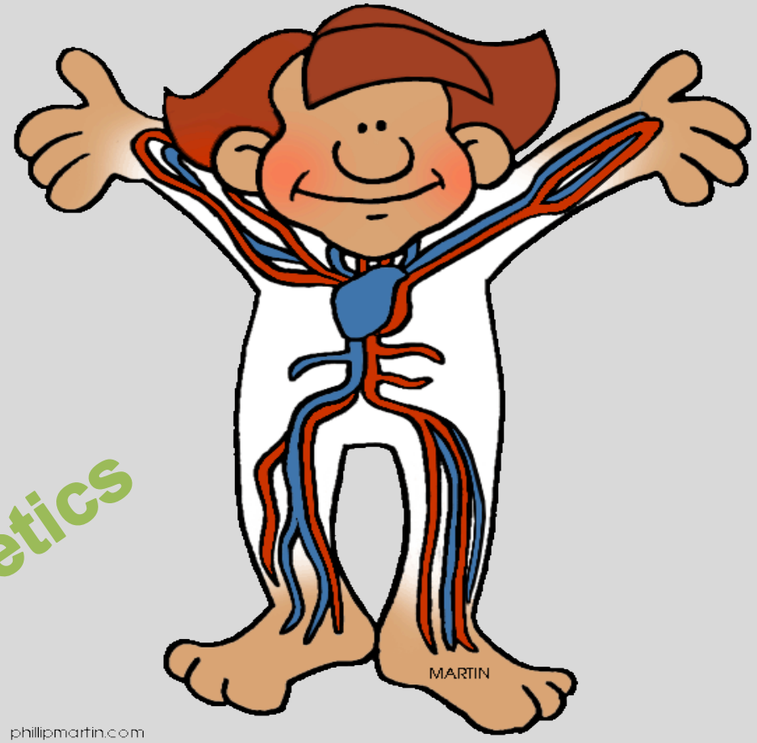
pharmacodynamics

What the drug does to the body and how

What the body does to the drug and how

pharmacokinetics



Learning objectives for Pharmacodynamics Part 1.

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After completing ScholarRx Bricks, Guided Reading Questions (GRQs), Practice Questions, and optional preparation materials, students will be able to:

1. Apply the physiology of receptors, effectors, and signaling mechanisms to pharmacology.
2. Define all terms listed in the handout and give examples of the specific actions for therapeutic drug effects.
3. Relate how the physicochemical characteristics (structural features) of a drug determine its ability to initiate a cellular effect (the effector mechanism).
4. Correlate drug concentration, receptor occupancy, and the magnitude of pharmacologic response by comparing dose-dependent therapeutic and toxicologic responses.
5. Describe the concepts of intrinsic activity, affinity, potency and efficacy by comparing the graded dose-response curves of two or more drugs.

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Preparation Materials (links are in the CPG and on the next slide)

Required

- ScholarRx Bricks | Practice Questions

Optional materials:

- Dr. Goldstein's Notes handout | Videos lectures | Guided reading questions

SUGGESTIONS:

- ***Use the resources that work best for you.***
- ***You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)***
- ***Work through the GUIDED READING QUESTIONS with pen/pencil and paper.***

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- ***Practice questions (not graded): Simple Recall and Case Vignettes***

Links

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Scholar Rx Bricks:

Cellular and Molecular Biology: Cell signaling https://exchange.scholarrx.com/brick/cell-signaling

General Pharmacology:

Pharmacology: Foundations and Frameworks https://exchange.scholarrx.com/brick/pharmacology-foundations-and-frameworks

Receptor Agonists and Antagonists https://exchange.scholarrx.com/brick/receptor-agonists-and-antagonists

Enzymes as Drug Targets https://exchange.scholarrx.com/brick/enzymes-as-drug-targets

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 1: Introduction > The Nature of Drugs
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281746718
and
Chapter 2: Drug Receptors & Pharmacodynamics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281746891

THE REVIEW BOOKS BELOW INCLUDE PRACTICE QUESTIONS.

Access Medicine Katzung's Pharmacology: Examination and Board Review, 14e, 2024; Chapter 1: Introduction > The Nature of Drugs
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285588535
and
Chapter 2: Drug Receptors & Pharmacodynamics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285588872

LWW Health Library Premier Basic Sciences, Lippincott Illustrated Reviews: Pharmacology, 8e, 2023: Chapter 2: Drug-Receptor Interactions and Pharmacodynamics
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253325200&bookid=3222

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Questions help learning. Questions help to master a topic.

1. **Guided Reading Questions** are intended to help you identify what you NEED to know.
   - Other information in the reading provides context to help you understand concepts within the big picture.
2. **Practice Questions** are for your own assessment of your learning – for applying what you have learned in the context of clinical case vignettes.
   - Practicing through case vignettes will help you bridge pharmacology science and pharmacotherapeutics (clinical concepts).
3. **Write down your own questions** as you study. This practice helps you identify where you are strong and where you weak so you can focus your efforts.

Brown, Roediger, and McDaniel. *Make It Stick The Science of Successful Learning*. Belknap Press of Harvard University Press, 2014

Tips for effective LEARNING (not rote memorizing).

- Identify and define key ideas/concepts.
- Rephrase MAIN ideas in your OWN WORDS.
- Convert MAIN points to questions.
- Relate the ideas to what you already know.

Techniques:

- Spacing your practice – reviewing material and questions after a period of time improves learning by giving your mind time to make connections.
- Mixing multiple subjects (interleaving) while you are studying improves learning and problem solving skills by forcing the brain to continually retrieve knowledge.
- Use / invent memory devices (mnemonics) to help you remember.

Brown, Roediger, and McDaniel. *Make It Stick The Science of Successful Learning*. Belknap Press of Harvard University Press, 2014

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Cell biology:
transporters
receptors
effectors

$$D + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} DR \longrightarrow \text{response}$$

Physicochemical characteristics
of a drug determine
drug movement and mechanisms

EC_{50}
K_d

Intrinsic activity
Efficacy
Potency

PHARMACODYNAMICS
the effects of drugs on the body

Graded Dose-Response
Curves
the drug's effect as a
function of its concentration

Agonists
Antagonists

Classical and Two-State
Receptor Occupancy Models

Pharmacodynamic Variability
in a population
Quantal Dose-Response
relationships

Dose-Concentration-Effect
relationship

$TI=LD_{50}/ED_{50}$

Definitions:

Terms you need to know to understand pharmacodynamics

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Drug	Law of Mass Action	Agonist / Full agonist
Pharmacodynamics	EC_{50} | K_d	Partial agonist
Pharmacokinetics	Receptor occupancy models:	Antagonist
Pharmacogenomics	Classical model	Neutral antagonist
Receptor	Two-state model	Inverse agonist
Effector	Constitutive activity	Competitive antagonist
Structure-activity relationship	Intrinsic activity	Noncompetitive antagonist
Receptor affinity	Efficacy	Uncompetitive antagonist
Target specificity	Potency	Physiological antagonist
Spare receptors	Allosteric binding	Chemical antagonist
Receptor desensitization	Tachyphylaxis	Tolerance
Receptor downregulation	Receptor upregulation	Supersensitivity
Therapeutic index	Therapeutic window	Margin of safety
LD_{50}/ED_{50}	TD_{50}/ED_{50}	LD_1/ED_{99} x100

What you need to know

- DEFINITIONS of terms used in pharmacology.
- Physicochemical characteristics of a drug determine its ability to move through the body and initiate a cellular effect – structure activity relationship and the molecular mechanisms of drug action.
- The molecular mechanisms of a drug's movement through the body and its actions are explained by physiological transporters, receptors, and effector mechanisms. Duration of drug action may result from dissociation of the drug from the receptor, activation of second messengers, synthesis of new receptors following destruction of covalent drug-receptor complexes, and desensitization of receptor effector systems.
- Drug-receptor interactions are described in quantitative terms using graded dose-response curves, to compare efficacy and potency of drugs and to determine appropriate dosage ranges for patients.
- The drug dose determines the concentration of drug in plasma, which determines the concentration of drug at the site of action, which determines the magnitude of pharmacologic effect, as reflected on graded dose-response curves.

What you need to know

- The drug concentrations at which the effect and receptor occupancy is half-maximal are denoted by EC_{50} and K_d, respectively.
- The hyperbolic relation of EC_{50} and K_d resembles the law of mass action, which describes the association between two molecules of a given affinity. It suggests that drug agonists act by binding (occupying) a distinct class of biologic molecules having affinity for the drug.
- The graded dose-response and the graded dose-receptor relationship assumes that the magnitude of the response to a drug is proportional to the concentration of receptors that are bound.
- Efficacy and potency are parameters that can be deduced from the graded dose-response curve.
- Some drugs can elicit a maximal response by occupying a fraction of the receptors in the total receptor pool. The remaining unbound receptors are referred to as “spare receptors”.

Physicochemical characteristics of a drug determine its ability to move through the body and initiate a cellular effect

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Structural features:
size, shape, chirality, electrical charge, and lipid solubility

Structure-Activity Relationship

Pharmacokinetic properties

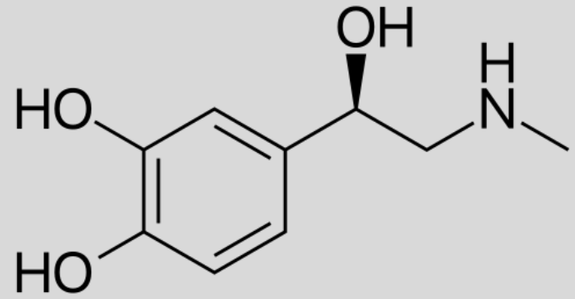
Determine the drug's ability to be **absorbed**, to **distribute** to the site of action, be **metabolized** and be **excreted**

Pharmacodynamic properties

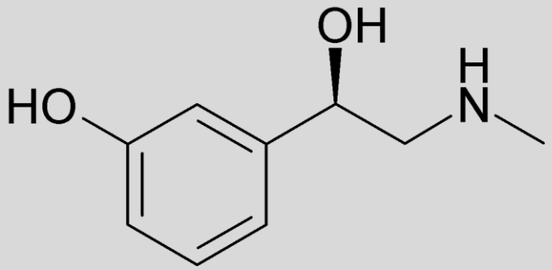
Determine **receptor specificity**, **receptor affinity** and **intrinsic activity**

Structure-Activity Relationship

- Structure-activity relationship is the **relationship** between the chemical or 3D **structure** of a molecule and its biological **activity**.
- In the example at the right, epinephrine is a natural hormone. Phenylephrine is a synthetic chemical with a similar structure and similar action.



epinephrine



phenylephrine

Molecular Mechanisms of Drug Action

the interaction of a drug with its target

brings about a change in biologic function as a result of binding to that receptor

produces a pharmacologic effect

1) activates biochemical and physiological changes ***characteristic of the receptor***

OR

2) blocks receptor without producing a response

Duration of Action (pharmacodynamic mechanisms)

A drug's action may persist until:

- Dissociation of the drug from the receptor, which automatically terminates the effect
- Activation of second messengers and signal transduction
- Drug-receptor complex is destroyed and new receptors or enzymes have been synthesized, in the case of covalent (irreversible) drug-receptor interactions
- Receptor-effector systems incorporate desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods.

PHARMACODYNAMICS

Quantitative aspects

Dose-response curves

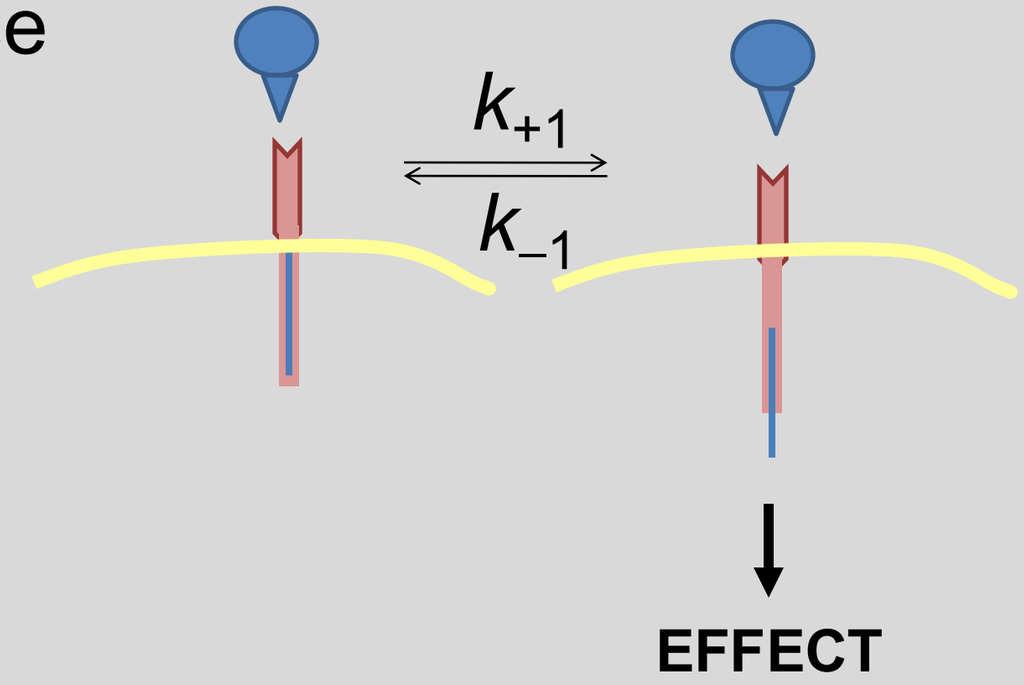
Receptor occupancy theory assumes that the portion of occupied receptors is related to the effect of the drug. Its basis is in the Law of Mass Action.

- Relationship between drug concentration and pharmacologic response:

$$D + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} DR \longrightarrow \text{response}$$

The number (concentration) of receptors [*R*] occupied by a drug depends on the:

1. drug concentration, [*D*],
2. drug-receptor association rate, k_{+1},
3. drug-receptor dissociation rate, k_{-1}

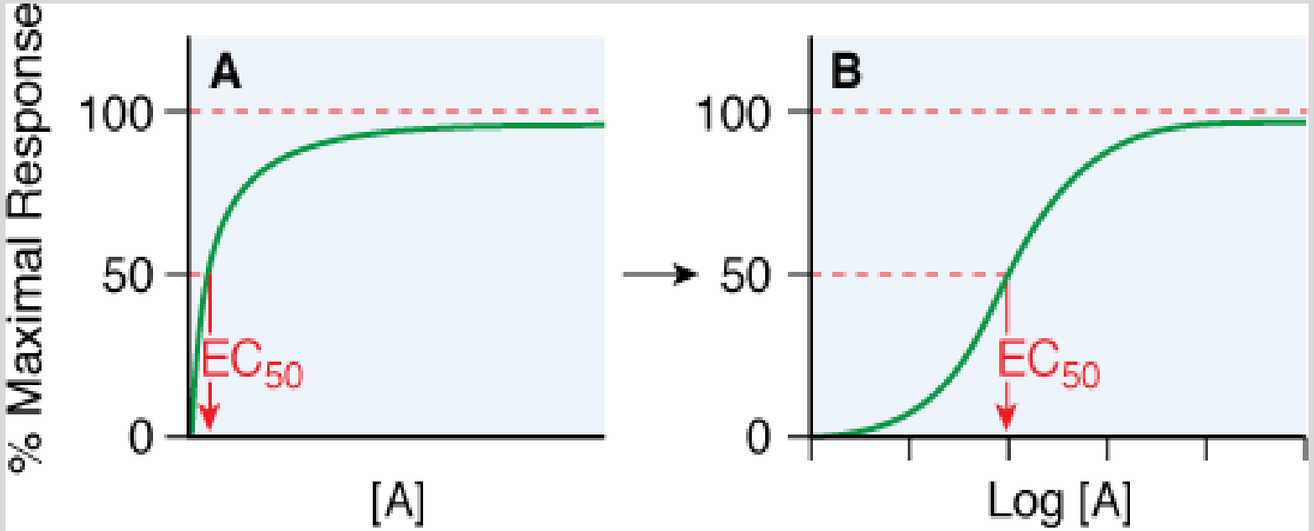


Equilibrium binding

- At equilibrium: $k_{+1} \cdot [D] \cdot [R] = k_{-1} \cdot [DR]$
- **Equilibrium dissociation constant (K_d)**: $K_d = \frac{[D][R]}{[DR]} = \frac{k_{-1}}{k_{+1}}$
  - Half the receptors are free and half are bound to drug
- **K_d represents the drug concentration required to saturate 50% of the receptors**
- **Affinity constant** – the reciprocal of K_d: $K_a = \frac{1}{K_d}$
  - The smaller the K_d, the greater the affinity.

Graded Dose-Responses Curves

The effect of a drug as a function of its concentration



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Plotting the data on a logarithmic concentration axis
↓
sigmoid curve
↓
simplifies mathematical manipulation of the dose-response data

EC_{50}: the concentration of drug that produces 50% of maximal response

Concentration-Effect & Receptor Binding Curves

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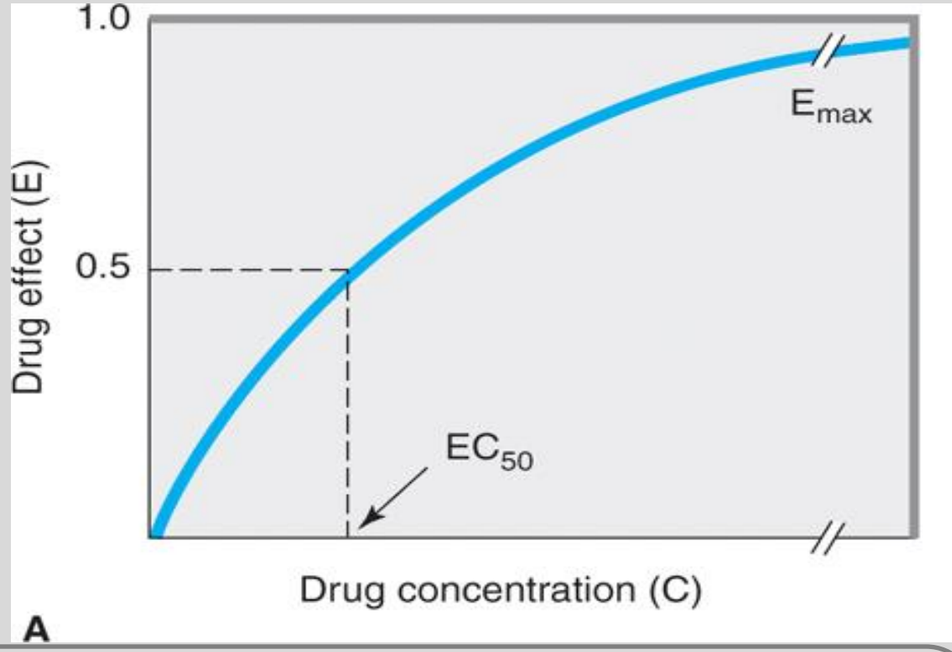
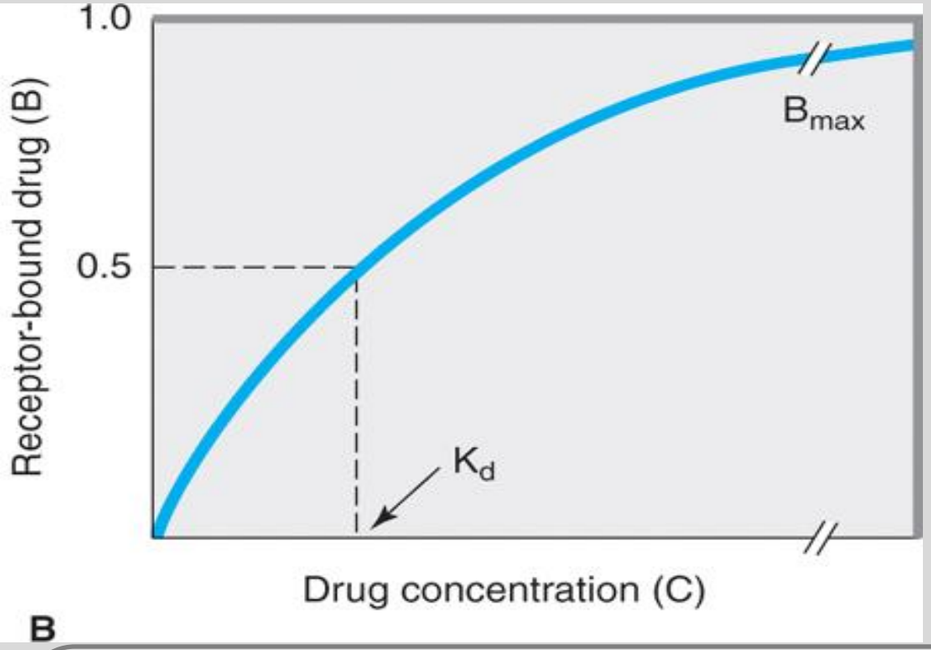
Drug Concentration-Effect Relationship



Drug Concentration-Receptor Occupancy Relationship

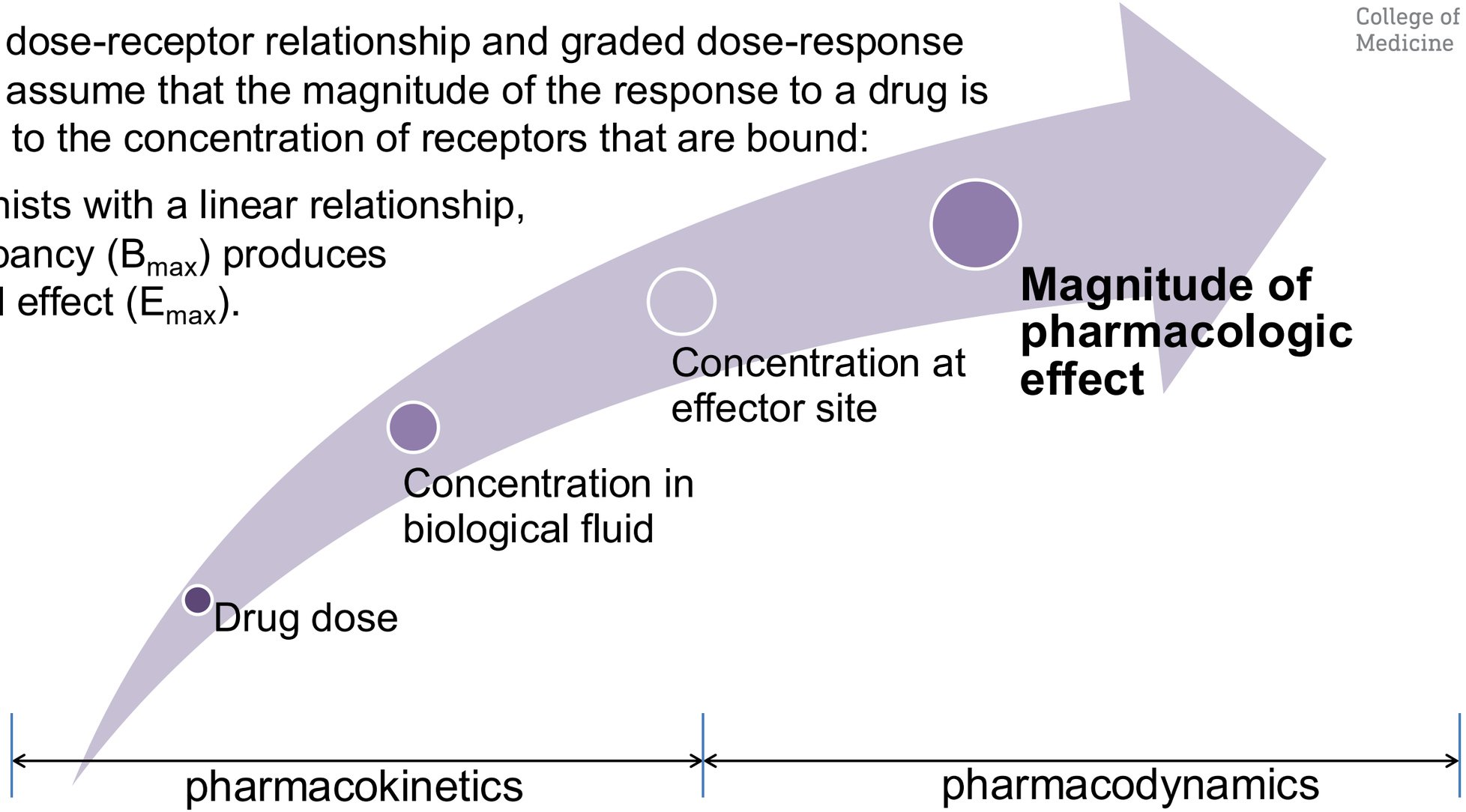


EC_{50}: Concentration of drug that produces 50% of maximal response
E_{max}: Maximal effect of agonist

K_d: Concentration of free drug at which half-maximal binding is observed
B_{max}: total concentration of receptor sites

The graded dose-receptor relationship and graded dose-response relationship assume that the magnitude of the response to a drug is proportional to the concentration of receptors that are bound:

For full agonists with a linear relationship, 100% occupancy (B_{max}) produces the maximal effect (E_{max}).



Intrinsic Activity | Efficacy | Potency

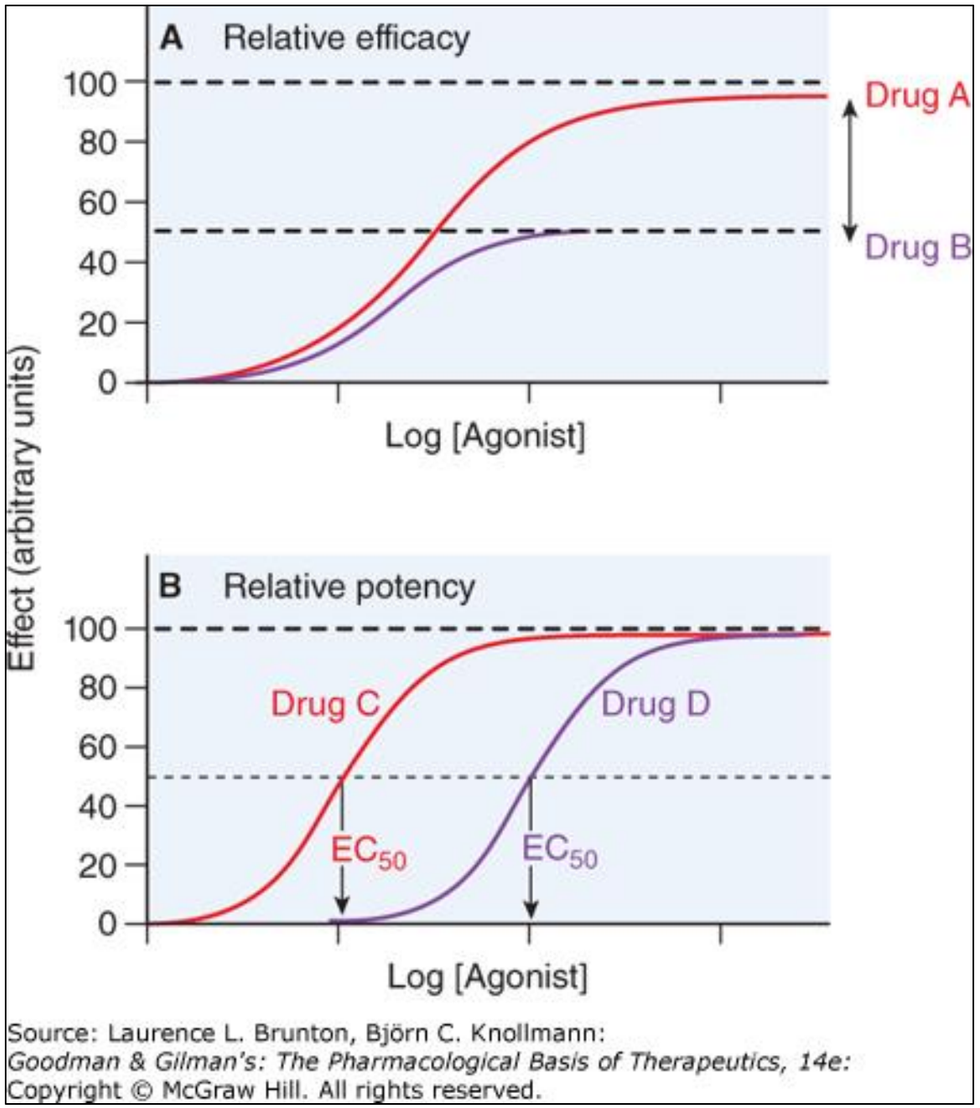
Intrinsic activity:
The ability of a drug bound to its receptor to activate downstream effector mechanisms

Efficacy:
The quantitative ability of a drug to elicit a physiologic response when it interacts with a receptor (it is related to the drug's intrinsic activity)

Potency:
The concentration of drug required to produce an effect (it is related to the drug's affinity for its target)

Please note:
In everyday language, the word ***efficacy*** means ***effective*** → ***'therapeutically useful activity'*** of any drug, both agonists or inhibitors.

Relative Efficacy and Relative Potency

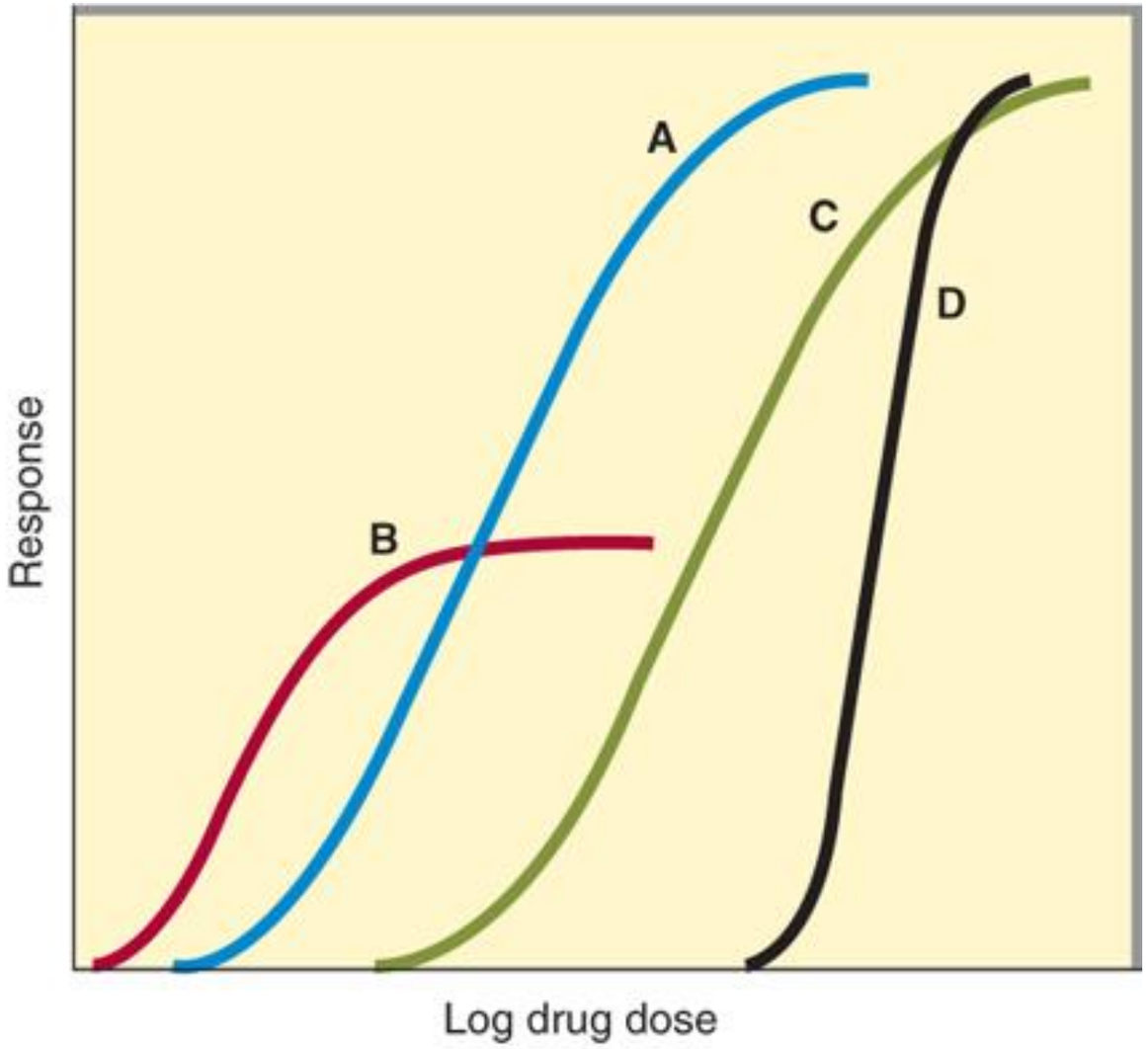


- **Efficacy:** The observed maximal responses of Drug A and Drug B binding to the same receptor is a function of their relative intrinsic activity (efficacy)
  - **the drug with greater efficacy produces a greater magnitude of effect than the drug with lesser efficacy**
- **Potency:** The relative potency of two agonists, Drug C and Drug D, obtained in the same tissue (same receptor) is a function of:
  - **their relative affinities**

Two ways of quantifying agonism.1. The relative efficacy of two agonists (Drug A = red line; Drug B = purple line) for a given type of receptor in the same cell or tissue is evaluated based on a comparison of responses. The asymptotic response of Drug A is two times that of Drug B; hence, Drug A is twice as efficacious as Drug B. 2. The EC_{50} of Drug C is one-tenth that of Drug D; hence, Drug C is 10-fold more potent than drug D.

Slide adapted by LG

Shape of Dose-response Curves



- Drugs A and B are more potent than drugs C and D.
- Drug B is more potent than Drug A but Drug A has a larger maximal efficacy.
- Drugs A, C, and D have equal maximal efficacy.
- Drug D has a very steep dose-response curve, which may have clinical consequences if the upper portion represents an undesirable magnitude of response, such as coma caused by a sedative hypnotic – there are increasingly higher risks of toxic responses with relatively small increases in dose.

Graded dose-response curves for four drugs, illustrating different pharmacologic potencies and different maximal efficacies.

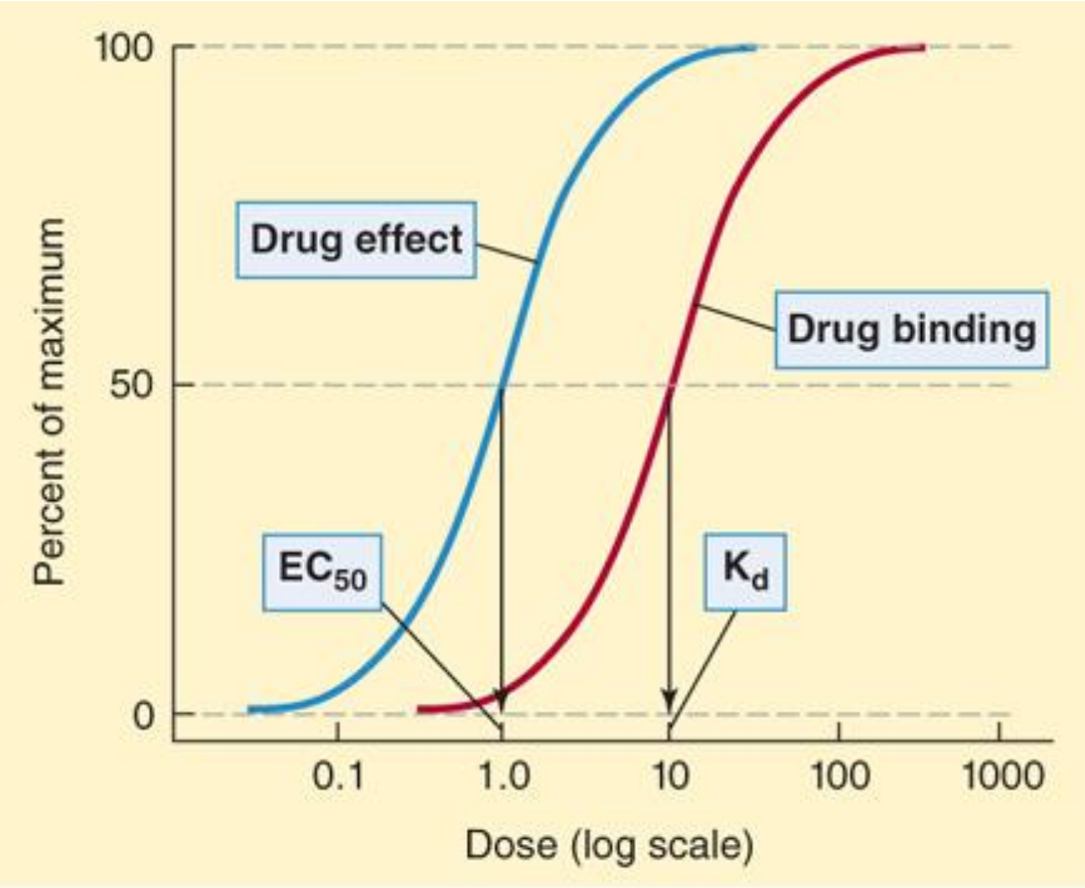
Citation: Chapter 2 Drug Receptors & Pharmacodynamics, Todd W. Vanderah. *Katzung's Basic & Clinical Pharmacology, 16th Edition;* 2024, Figure 2-15.
Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3382&sectionid=281746891

Slide adapted by LG

Spare Receptors

- Receptors are said to be “spare” for a given pharmacologic response if it is possible to elicit a ***maximal biologic response*** at a concentration of agonist that does not result in occupancy of the full complement of available receptors.

Spare: a reserve supply – as in spare tire or spare cash



Source: M. Kruidering-Hall, B. G. Katzung, R. L. Tuan, T. W. Vanderah: Katzung's Pharmacology Examination & Board Review, 14th Edition

Spare Receptors are said to exist if the maximal drug response (E_{max}) is obtained at less than 100% occupation of the receptors (B_{max}).

Said another way,

- Only a fraction of the total receptors are needed to elicit a maximal biologic response.

Thus,

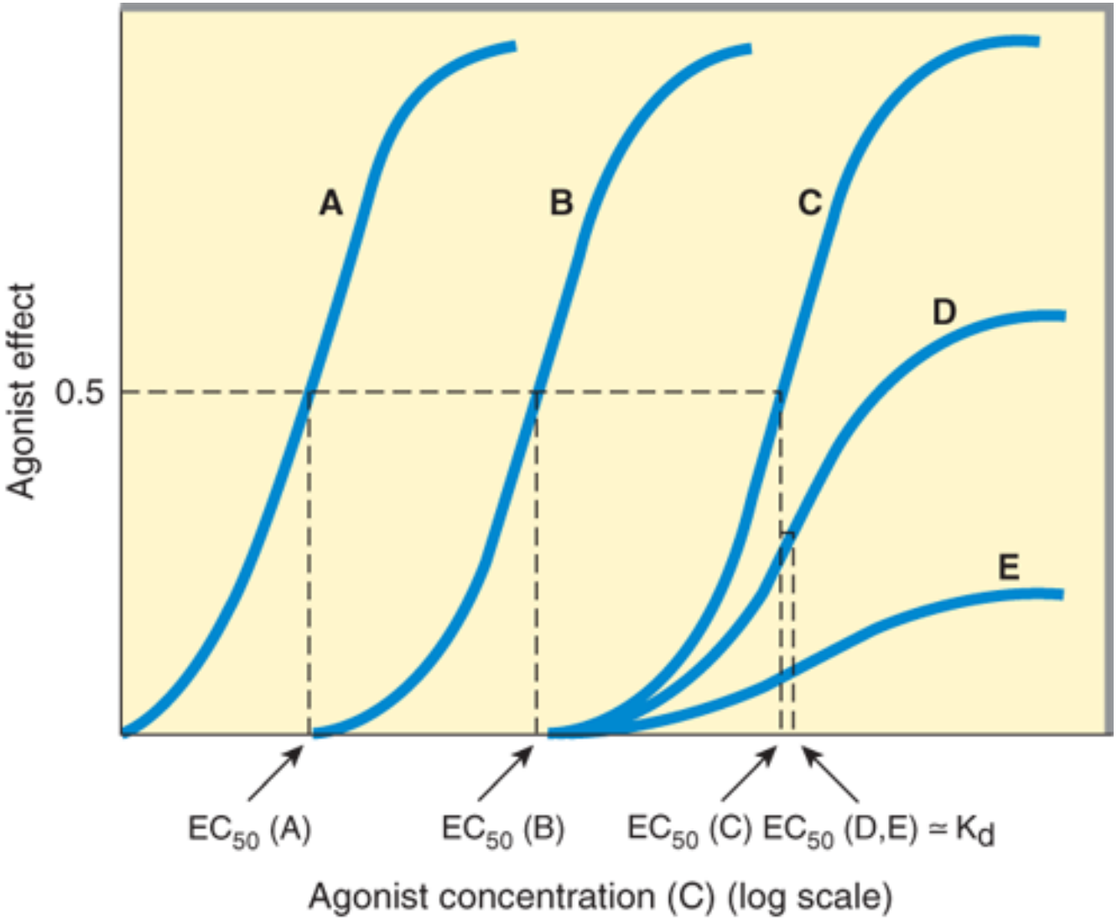
- **The remaining receptors that are not bound by agonist are referred to as spare receptors.**

In a system with spare receptors, the EC_{50} is lower than the K_d, indicating that to achieve 50% of maximal effect, less than 50% of the receptors must be activated. This might result from one of two mechanisms. First, the duration of the *effector activation* may be much greater than the duration of the *drug-receptor interaction*. Second, the actual number of receptors may exceed the number of effector molecules available. The presence of spare receptors increases sensitivity to the agonist because the likelihood of a drug-receptor interaction increases in proportion to the number of receptors available.

Citation: Citation: Chapter 2 Pharmacodynamics, Marieke Kruidering-Hall, Bertram G. Katzung, Rupa Lalchandani Tuan, Todd W. Vanderah. *Katzung's Pharmacology Examination & Board Review, 14th Edition;* 2024, Figure 2-3. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3461&sectionid=285588872

Slide adapted by LG

Spare receptors can be demonstrated experimentally by using an irreversible antagonist to prevent binding of the agonist to a proportion of available receptors.



A: Agonist response in absence of antagonist

B: Low concentration of antagonist: shift to right, maximal response preserved

Even with the higher concentration of agonist, activation of only a fraction of receptors in the receptor pool is adequate to achieve maximal response: the agonist's EC_{50} is still < K_d.

C: Larger concentration of antagonist: shift to right, max response preserved

The number of remaining receptors is just enough to achieve the maximal response: the agonist's $EC_{50} \approx K_d$.

D, E: Higher antagonist concentrations reduce the number of available receptors; response is diminished.

the agonist's $EC_{50} \approx K_d$.

Citation: Chapter Chapter 2 Drug Receptors & Pharmacodynamics, Todd W. Vanderah. *Katzung's Basic & Clinical Pharmacology, 16th Edition;* 2024, Figure 2-2. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3382&sectionid=281746891

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Move the terms next to the correct definitions.

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The actions of the body on the drug	
The actions of the drug on the body	
The branch of a science that deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems	
The development of drugs based on knowledge of the three-dimensional structure of the receptor site	
The relation of the individual's genetic makeup to his/her/their response to specific drugs	
The science of substances used to prevent, diagnose, and treat disease	
A specific molecule in the biologic system that plays a regulatory role	
A substance introduced to the body that brings about a change in biologic function through its interactions with body components	

Drug
Pharmacodynamics
Medical pharmacology
Toxicology
Receptor
Pharmacokinetics
Pharmacogenomics
Rational drug design

Move the terms next to the correct definitions.

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A drug that binds to and activates a receptor but does not evoke a maximal response, no matter how high the concentration of drug	
A drug that binds to a receptor, competes with and prevents binding by other molecules	
The relative ability of a drug-receptor complex to produce the maximal functional response	
A drug that has a much stronger affinity for the R_i than for the R_a state and stabilizes a large fraction in the R_i–D pool, reducing constitutive activity	
In the absence of any agonist, some of the receptor pool must exist in the activated (R_a) form some of the time and may produce the same physiologic effect as agonist-induced activity	
A drug that binds to and activates the receptor in some fashion, which directly or indirectly brings about the effect	
A drug that directly activates a receptor by binding to a receptor site distinct from the primary site	
A drug that binds a receptor at a site distinct from the primary site, inhibits the action of the agonist, and is not overcome by increasing the dose of the agonist	

Intrinsic efficacy | Agonist | Antagonist | Inverse agonist | Partial agonist

Allosteric activator | Allosteric inhibitor | Constitutive activity

SUMMARY OF PHARMACODYNAMICS CONCEPTS

Part 1

Pharmacology is the body of knowledge concerned with the action of chemicals on biologic systems.

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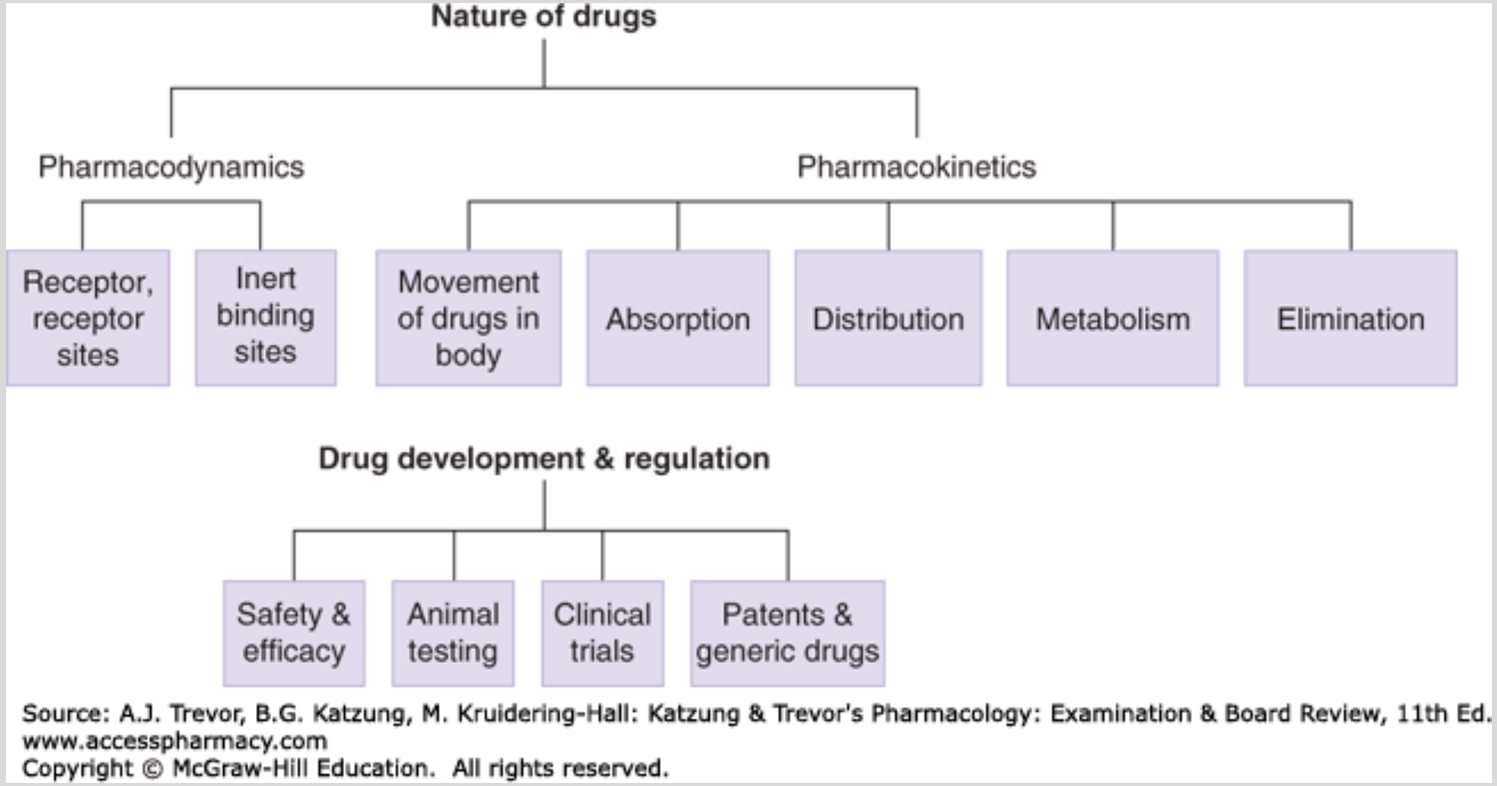
1. Pharmacodynamics is the study of the biochemical, cellular, and physiologic effects of drugs and their mechanisms of action. “What the drug does to the body, and how it does it.”
2. Pharmacokinetics is the study of the movement and fate of drugs in the body: absorption, distribution, metabolism, and excretion. “What the body does to the drug, and how it does it.”

- Knowledge of biochemical, cellular, physiologic, and pathologic processes is essential for understanding pharmacodynamics and pharmacokinetics.
- Knowledge of pharmacology is essential for the safe and effective use of drugs:

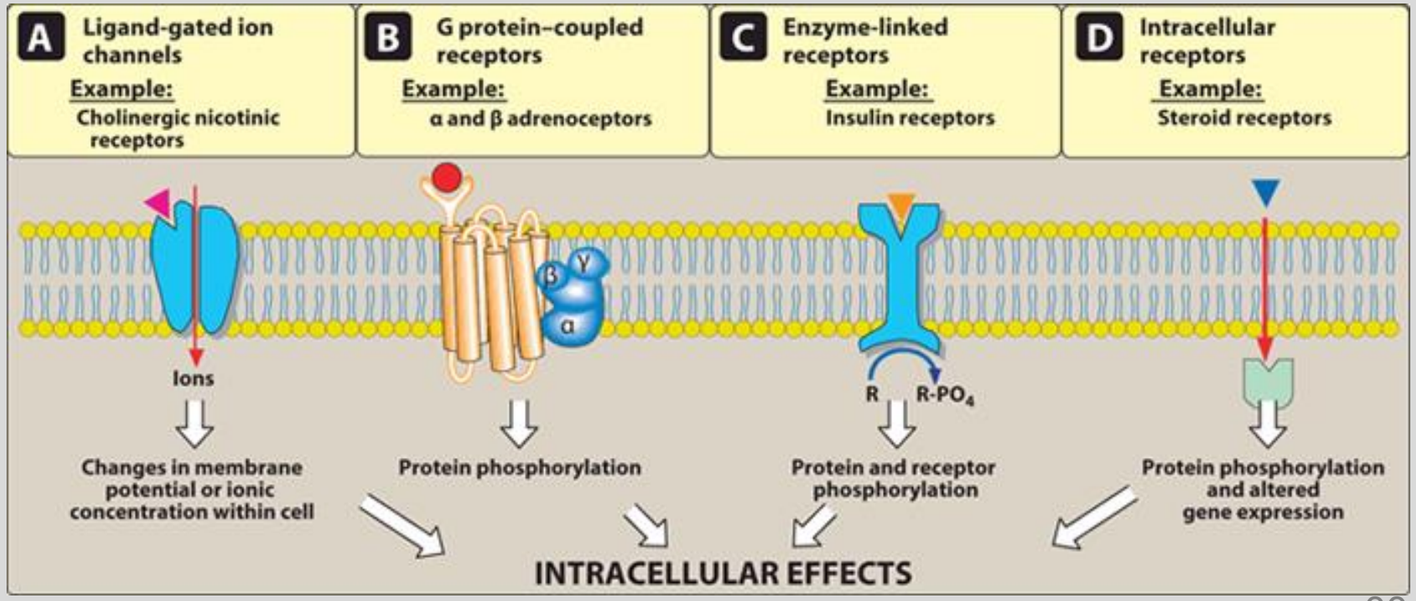
Optimizing drug therapy in the individual patient.



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

The Nature of Drugs: Structure and Function

- The physicochemical characteristics of a drug determines its ability to move through the body and initiate a cellular effect.
- The physicochemical characteristics of a drug that predict its movement and availability at sites of action are its molecular size, shape, and chirality, degree of ionization, and relative lipid solubility of its ionized and non-ionized forms.
- The structure-activity relationship is the **relationship** between the chemical or 3D **structure** of a molecule and its biological **activity**.
- The interaction of a drug with its receptor is the fundamental event that initiates the action of the drug.



Pharmacodynamics concepts

- Drugs interact with receptors to produce a change in the state (conformation) of the receptor, which transduces a physiologic effect.
- The molecular interaction with the receptor can be modeled mathematically and obeys the Law of Mass Action.
- The binding of a drug and receptor determines the quantitative relationship between dose and effect.
- Mutual affinity of drug and receptor determines the quantitative relationship between dose and effect.
- Traditional receptor occupancy theory rests on the assumption that the proportion of occupied receptors is related to the effect of the drug – for full agonists, 100% occupancy (B_{max}) produces the maximal effect (E_{max}), a linear relationship.
- For some receptors, a biologic response (E_{max}) may be achieved before full receptor occupancy: $EC_{50} < K_d$. The fraction of unoccupied receptors are called spare receptors.

Answers to the matching.

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The actions of the body on the drug	Pharmacokinetics
The actions of the drug on the body	Pharmacodynamics
The branch of a science that deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems	Toxicology
The development of drugs based on knowledge of the three-dimensional structure of the receptor site	Rational drug design
The relation of the individual's genetic makeup to his/her/their response to specific drugs	Pharmacogenomics
The science of substances used to prevent, diagnose, and treat disease	Medical pharmacology
A specific molecule in the biologic system that plays a regulatory role	Receptor
A substance introduced to the body that brings about a change in biologic function through its interactions with body components	Drug

Answers to the matching quiz.

A drug that binds to and activates a receptor but does not evoke a maximal response, no matter how high the concentration of drug	Partial agonist
A drug that binds to a receptor, competes with and prevents binding by other molecules	Antagonist
The relative ability of a drug-receptor complex to produce the maximal functional response	Intrinsic efficacy
A drug that has a much stronger affinity for the R_i than for the R_a state and stabilizes a large fraction in the R_i–D pool, reducing constitutive activity	Inverse agonist
In the absence of any agonist, some of the receptor pool must exist in the activated (R_a) form some of the time and may produce the same physiologic effect as agonist-induced activity	Constitutive activity
A drug that binds to and activates the receptor in some fashion, which directly or indirectly brings about the effect	Agonist
A drug that directly activates a receptor by binding to a receptor site distinct from the primary site	Allosteric activator
A drug that binds a receptor at a site distinct from the primary site, inhibits the action of the agonist, and is not overcome by increasing the dose of the agonist	Allosteric inhibitor

References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e, 2023; Chapter 3: Pharmacodynamics: Molecular Mechanisms of Drug Action
- Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 1: Introduction > General Principles of Pharmacology: the section on The Nature of Drugs THROUGH Pharmacodynamic Principles
- Access Medicine Katzung's, Chapter 2.: Drug Receptors & Pharmacodynamics

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Lecture Feedback Form:

https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R

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Pharmacodynamics Part 2:

- Quantifying Agonism and Antagonism
- Receptor Dynamics
- Pharmacodynamic Variability in Populations

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I am available to groups and individuals for pharmacology help and discussions by appointment.

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Learning objectives for Pharmacodynamics Part 2.

After completing preparation materials, students should be able to:

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1. Compare and contrast the actions and effects of agonists and antagonists as illustrated by specific concentration-effect curves (*dose-response relationships*).
2. Define agonists and antagonists in the context of classical receptor occupancy model and two-state receptor occupancy model.
3. Differentiate competitive antagonists, noncompetitive antagonists, negative and positive allosteric modulators, and spare receptors (Part 1) as demonstrated in experimental models.
4. Relate drug action, receptor occupancy, receptor response, and receptor regulation based on the concentration-effect curves and receptor binding of agonists and antagonists.
5. Explain pharmacodynamics variability in a population and calculate therapeutic index when given information from quantal dose-response curves.

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Preparation Materials (links are in the CPG and on the next slide)

Required

- ScholarRx Bricks | Practice Questions

Optional materials:

- Dr. Goldstein's Notes handout | Videos lectures | Guided reading questions

SUGGESTIONS:

- ***Use the resources that work best for you.***
- ***You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)***
- ***Work through the GUIDED READING QUESTIONS with pen/pencil and paper.***

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- ***Practice questions (not graded): Simple Recall and Case Vignettes***

Links

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Scholar Rx Bricks:

Cellular and Molecular Biology: Cell signaling https://exchange.scholarrx.com/brick/cell-signaling

General Pharmacology:

Pharmacology: Foundations and Frameworks https://exchange.scholarrx.com/brick/pharmacology-foundations-and-frameworks

Receptor Agonists and Antagonists https://exchange.scholarrx.com/brick/receptor-agonists-and-antagonists

Enzymes as Drug Targets https://exchange.scholarrx.com/brick/enzymes-as-drug-targets

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 1: Introduction > The Nature of Drugs
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281746718
and
Chapter 2: Drug Receptors & Pharmacodynamics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281746891

THE REVIEW BOOKS BELOW INCLUDE PRACTICE QUESTIONS.

Access Medicine Katzung's Pharmacology: Examination and Board Review, 14e, 2024; Chapter 1: Introduction > The Nature of Drugs
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285588535
and
Chapter 2: Drug Receptors & Pharmacodynamics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285588872

LWW Health Library Premier Basic Sciences, Lippincott Illustrated Reviews: Pharmacology, 8e, 2023: Chapter 2: Drug-Receptor Interactions and Pharmacodynamics
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253325200&bookid=3222

RECEPTOR OCCUPANCY MODELS

- **The two-state receptor occupancy model** postulates that, in the absence of a ligand, a receptor assumes two conformational states – active (R_a) and inactive (R_i). Some receptors in the receptor pool must exist in the R_a form some of the time and produce constitutive (basal) activity. The extent to which an agonist shifts the equilibrium toward the active state is determined by the relative affinity of the drug for the two conformations.
  - Full agonists have a much higher affinity for the R_a conformation and stabilize it so that a large percentage of receptors in the pool are in the R_a-D complex which produces the full effect.
  - Partial agonists bind R_a with slightly greater affinity than R_i so only a submaximal response is produced no matter the dose.
  - Neutral antagonists bind R_a and R_i with equal affinity. The equilibrium is not altered. No change in activity is observed.
  - Inverse agonists stabilize a large percentage of receptors as R_i-D, which reduces basal activity.

- **The classical receptor occupancy model** of drug-receptor interactions postulates that receptors in a receptor pool are inactive unless activated by a ligand.
  - Agonists bind receptors and activate the receptor signaling pathway – agonists have affinity and intrinsic activity.
  - Antagonists bind receptors, do not activate signaling, and interfere with the agonist's ability to activate the receptor – antagonists have affinity, zero intrinsic activity, and block the agonist from activating the receptor.
- Antagonists are characterized as competitive antagonists, irreversible active site antagonists, and allosteric receptor modulators.
  - Competitive antagonists bind the active site. The effects are surmountable with high enough dose of the agonist. The dose-response curves are shifted rightward and E_{max} is not reduced.
  - Irreversible (noncompetitive) active site antagonists bind irreversibly or with very high affinity to the active site, which prevents the agonist from activating the receptor. The effects are insurmountable.
  - Negative allosteric modulators bind an allosteric site, which reduces the affinity and/or efficacy of the agonist.
  - Positive allosteric modulators enhance the affinity of the receptors for the agonists, enhancing the agonist effect.

Other mechanisms of drug antagonism:

- Physiologic (functional) antagonism describes counterbalancing actions of substances on different endogenous regulatory pathways mediated by different receptors.
- Chemical antagonists are non-receptor antagonists – compounds that directly interact with the agonist, modifying or sequestering it so it is not able to bind its receptor.

RECEPTOR DYNAMICS

- Cellular regulation of drug-receptor interactions (receptor dynamics) prevents overstimulation that could harm the cell or the entire organism. As a result of this physiologic regulation, many drugs show diminishing effects over time.

Diminished exposure with continuous or repeated exposure to an agonist:

- Receptor desensitization (insensitivity) occurs due to phosphorylation of the receptors, or other mechanisms, which decreases the coupling efficiency of receptors.
- Internalization and degradation of receptors, including bound ligands, decreases the number of receptors. This regulatory mechanism is called receptor downregulation.
- Tachyphylaxis is an acute, sudden decrease in response after continuous or repeated administration of a drug.

Receptor resensitization: After withdrawal of the agonist, the cells recover full responsiveness to a subsequent addition of agonist.

Receptor supersensitivity with continuous or repeated exposure to an antagonist:

- Increased expression of receptors can cause cells to be more sensitive to the agonist when the antagonist is withdrawn.

Other mechanisms of reduced response to drugs:

- Increased rate of drug metabolism due to drug-drug interaction or pharmacogenetic variabilities reduces systemic plasma concentrations, which may reduce the efficacy of the drug.
- Pharmacogenetic variabilities or disease states may alter the number and/or function of receptors, which can alter the individual's response to drugs.

PHARMACODYNAMIC VARIABILITY IN A POPULATION

- Individuals vary in the magnitude of their response to the same concentration of a single drug or to similar drugs, and a given individual may not always respond in the same way to the same drug concentration.
- Determining the dose of a drug that produces a particular effect in a large number of individuals (patients or experimental animals) can be useful in determining the margin of safety to be expected from a particular drug.
- Quantal dose response is a specified effect of a drug that is either present or absent in individuals in a population – an either-or (quantal) event. In a population, there is usually some variation in the dose needed to achieve a specified drug effect.
- The response elicited with each dose is plotted against the log dose of the drug.
- The curves can be used to describe median effective dose (ED_{50}), median lethal dose (LD_{50}), median toxic dose (TD_{50}), therapeutic index, margin of safety, and other parameters.

Receptor Occupancy Models
Agonists and Antagonists

Receptor occupancy models propose explanations of the activity of drugs at receptors.

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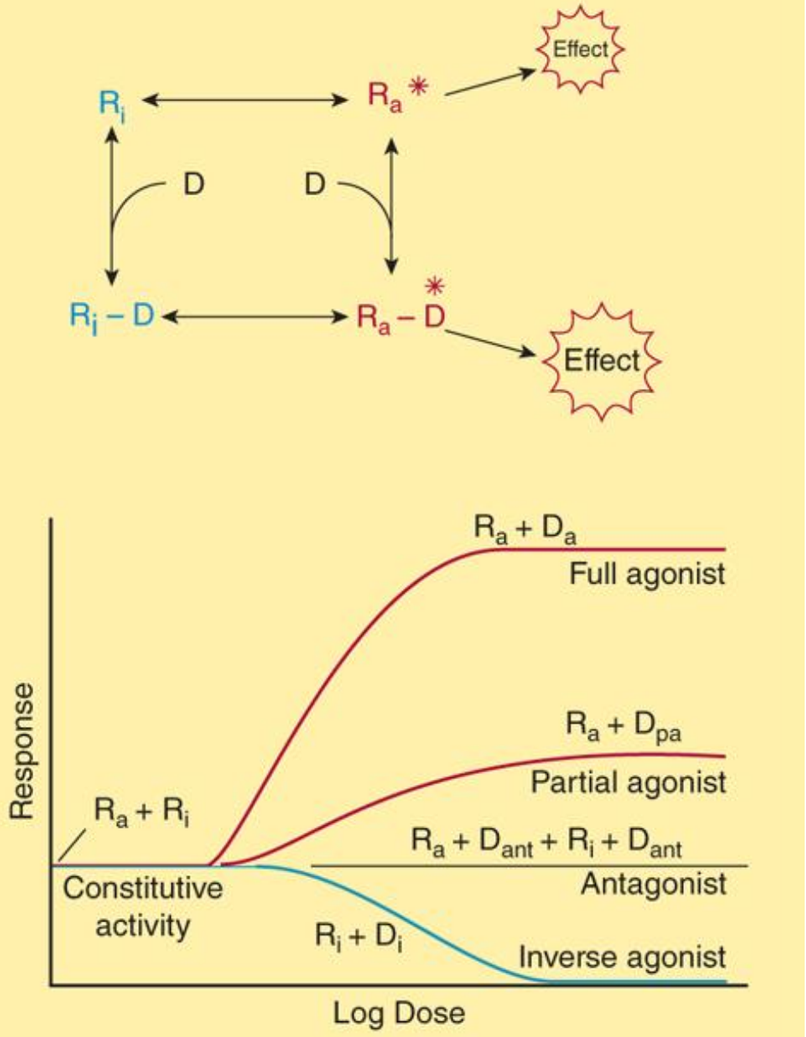
Two-State Receptor Occupancy Model postulates that the receptor assumes two conformational states – active and inactive – in the absence of a ligand.	**Classical receptor occupancy model** postulates that receptors in a receptor pool are quiescent unless activated by a ligand.
Even in the absence of any ligand, some of the receptors in the receptor pool must exist in the activated (R_a) form.	Agonists bind to receptors and ***stimulate*** the signal transduction pathways. ***Agonists have affinity & intrinsic activity.***
The receptor can activate downstream mechanisms that produce a small observable effect, even in the absence of a ligand. It has ***constitutive (basal) activity.***	Antagonists bind to receptors and ***inhibit*** the biological responses by interfering with the agonist's ability to activate receptor. ***Antagonists have affinity & zero intrinsic activity & block the agonist from occupying the site.***



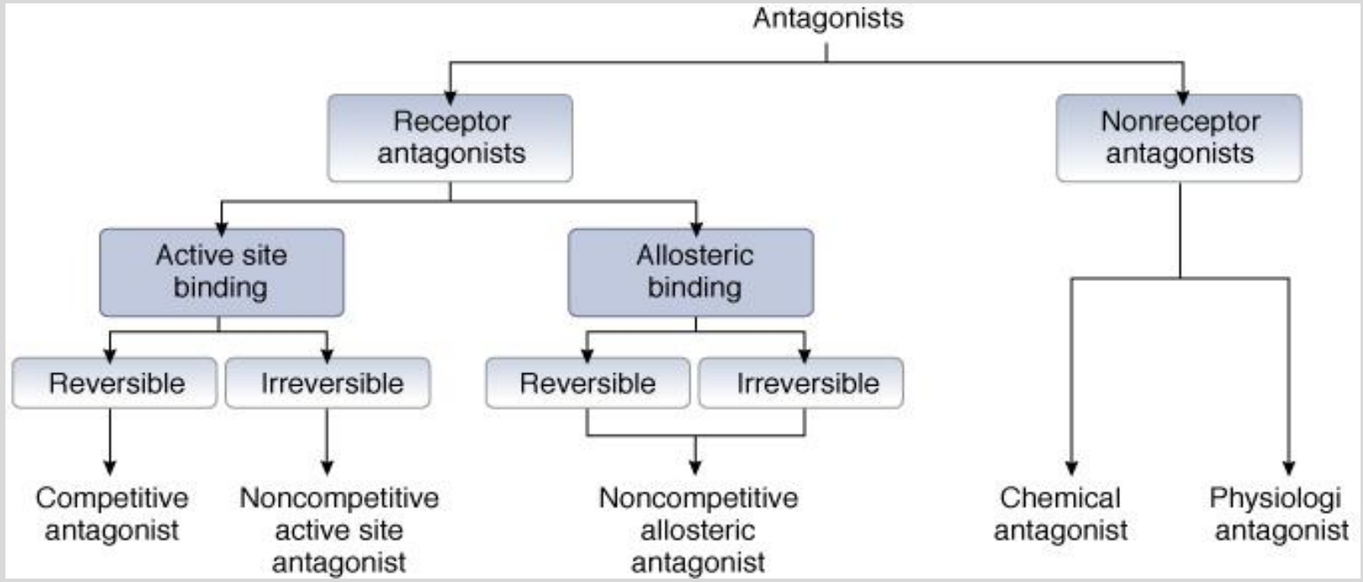
Two-state model of drug-receptor interaction. The hypothetical receptor is able to assume two conformations.

The receptor in the R_i conformation is inactive and produces no effect, even when combined with a drug molecule. In the R_a conformation, the receptor can activate downstream mechanisms that produce a small observable effect, even in the absence of drug (constitutive activity). In the absence of drugs, the two isoforms are in equilibrium, and the R_i form is favored.

- **Full agonists** have a much higher affinity for the R_a conformation and shift almost all of the receptors to the R_a-D pool, which can activate the receptor-effector systems to the maximal effect.
- **Partial agonists** have slightly greater affinity for R_a than for R_i. They do not stabilize the R_a configuration as fully as full agonists; a significant fraction of receptors exist in the R_i-D pool. They prevent the full agonist from accessing the site of action.
- **Neutral antagonists** have equal affinity for both receptor forms and maintain the same level of constitutive activity. The drug will appear to be without effect, but will block the agonist from accessing the site of action.
- **Inverse agonists** have a much higher affinity for the R_i form, stabilize a large fraction in the R_i-D pool, and reduce constitutive activity, resulting in an effects opposite those of the agonist.

Classical Receptor Occupancy Model
Classification of Antagonists

- Competitive antagonists compete for the same binding site as the agonist and affect the amount of agonist needed to achieve a maximal response.
- Noncompetitive antagonists reduce the magnitude of the maximal response that can be achieved by any amount of agonist without having an effect on the binding of the agonist to the receptor.



LWW Health Library Principles of Pharmacology, 2017 Figure 2-4: Antagonist Classification

- Physiologic antagonists are substances that act on different endogenous regulatory pathways mediated by different receptors and have opposite (counterbalancing) effects.
- Chemical antagonists are compounds that directly interact with the agonist, modifying or sequestering it so that the agonist cannot bind its receptors.

An antagonist binds the receptor but does not activate it.
An antagonist blocks the effects of the agonist.

Competitive antagonist: A drug that binds reversibly to the *agonist binding site* on the receptor and competes with the agonist for the binding site (Panel A, upper).

- Inhibitory effects are surmountable with increasing agonist dose.
- The agonist's concentration-effect curve shifts to the right. E*max* is not reduced

Irreversible active site antagonist: A drug that binds covalently (irreversibly) or with very high affinity (pseudo-irreversibly) at the same site as the agonist prevents the agonist from activating the receptor, even at high agonist concentrations, and depresses the agonists maximal response.

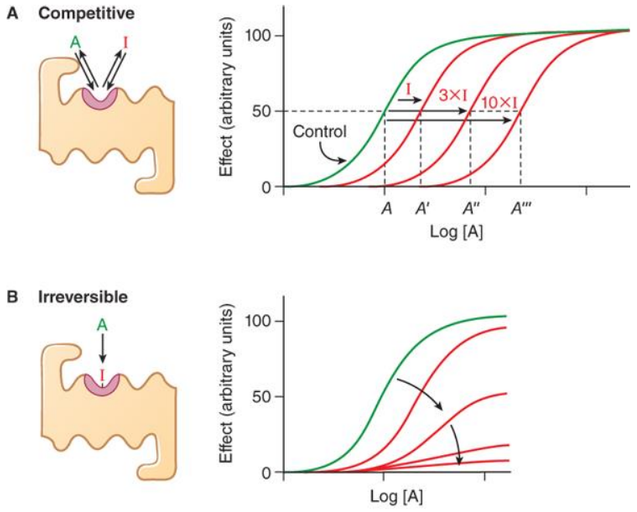
(Panel B, upper: As antagonist concentration increases, the agonist's dose-response curves shift rightward and downward, suggesting some degree of spare receptors.)

Positive allosteric modulator: A drug that binds to an allosteric site and *enhances the affinity* of the receptor for the agonist, increasing the agonist's effect.

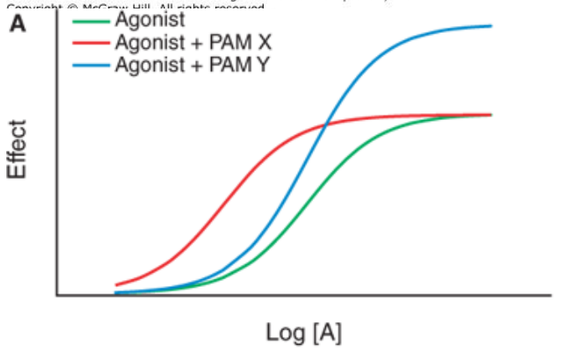
(Panel A, lower: PAM X, shifts the agonist's EC_{50} leftward, which increases the affinity/potency of the agonist. PAM Y increases the E_{max} for the agonist.)

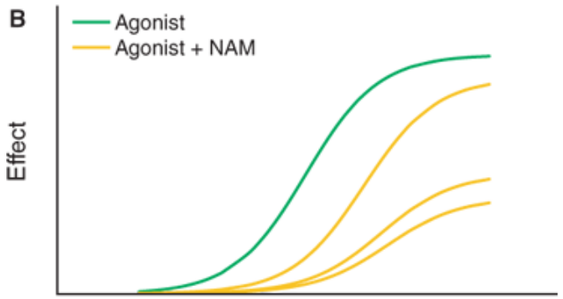
Negative allosteric modulator: A drug that binds to a site on the receptor other than the active site and reduces the affinity and/or the efficacy of the agonist. The EC50 may not be changed.

(Panel B, lower: In this set of dose-response curves, the negative allosteric modulator, NAM, has a negative impact on both EC_{50} and E_{max}, reducing affinity/potency and efficacy.)



Source: Laurence L. Brunton, Björn C. Knollmann: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:*





Slide adapted by LG

Citation: Chapter 3 Pharmacodynamics: Molecular Mechanisms of Drug Action, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e;* 2023, Figures 13-12 and 13-13. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=269715460 Accessed: June 05, 2023

Other Mechanisms of Antagonism

Physiologic (Functional) Antagonist

A substance that produces physiologic effects opposing the physiologic effects of another substance

- The functional actions on different regulatory pathways mediated by different receptors are opposite to each other.

Examples:

1. Insulin reduces blood sugar. Glucagon increases blood sugar.
2. Methacholine causes bronchoconstriction. Albuterol causes bronchodilation.

Chemical Antagonist

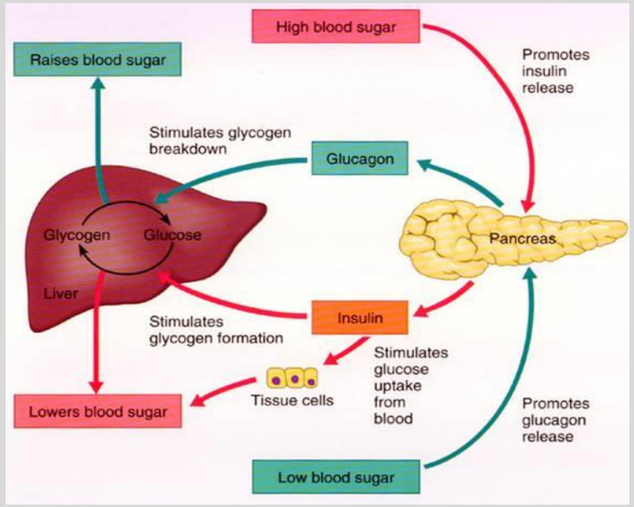
A compound that directly interacts with the agonist, modifying or sequestering it so that the drug is no longer capable of binding to its receptor.

- The product of the combination is inactive and excreted.

Examples:

1. Heparin is bound by protamine.
2. Divalent cations in antacids chelate tetracycline.
3. Cholestyramine is an cation exchange resin that sequesters many drugs in the gut, preventing absorption of that drug.

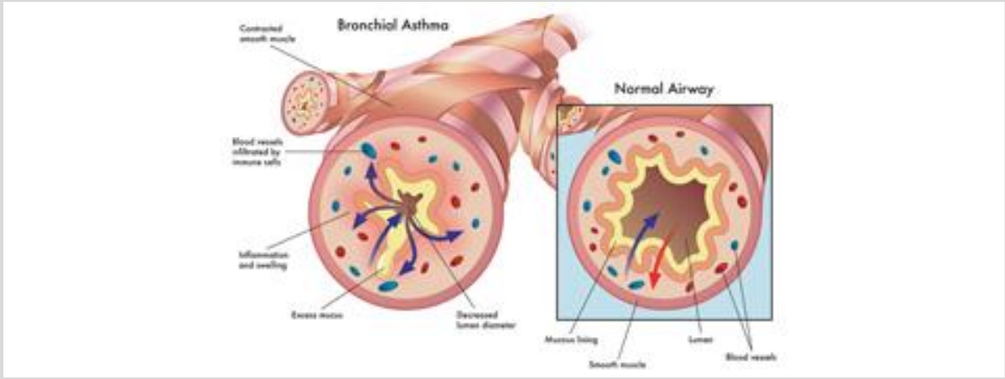
Example: The counterbalancing effects of physiologic (functional) antagonism



- Insulin lowers blood sugar by stimulating uptake of glucose by cells in the liver, skeletal muscle, and adipose tissue.
- Glucagon raises blood sugar by promoting glucose synthesis in the liver.

Clinical application: Glucagon may be administered for the treatment of severe hypoglycemia, such as from too much insulin.

- Methacholine (inhaled) is a cholinomimetic that activates muscarinic receptors in bronchial smooth muscle, which causes contraction – bronchoconstriction.
- Albuterol (inhaled) is a sympathomimetic that activates beta-2 receptors in bronchial smooth muscle, which causes relaxation – bronchodilation.

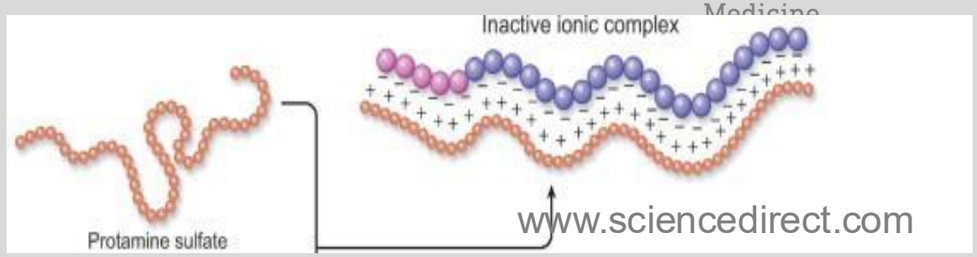


Clinical application:
Methacholine challenge is a test for bronchial hyperresponsiveness for the diagnosis of asthma.
Albuterol treats the asthma symptoms caused by the bronchoprovocation test by reversing the effects of methacholine.

Google images

Examples of Chemical Antagonists

- Positively charged protamine sulfate binds to negatively charged heparin in the bloodstream
- Heparin is not available to bind to its target
- Heparin's anticoagulant effect is neutralized



- Polyvalent metal ions chelate tetracycline forming a poorly absorbed complex.
- Antacids reduce absorption and reduce efficacy of tetracycline.

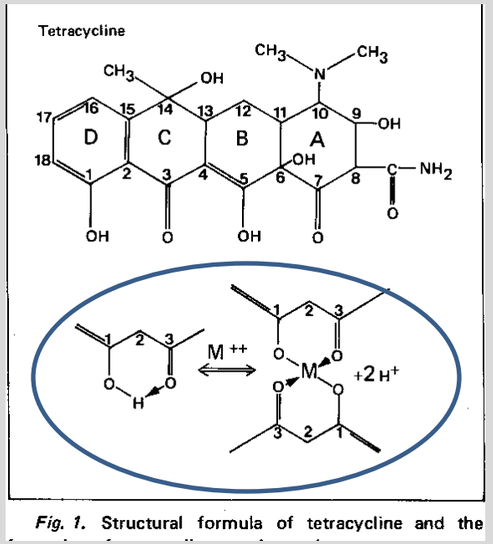
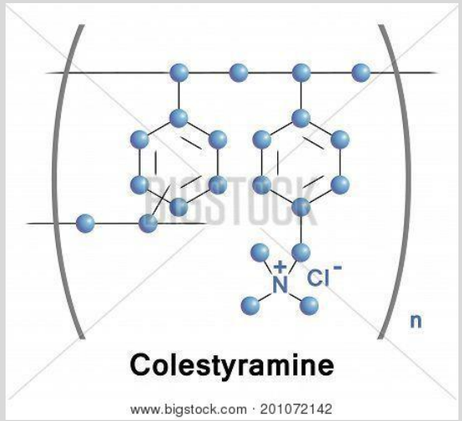


Fig. 1. Structural formula of tetracycline and the

- Cholestyramine is a strong cation exchange resin.
- Cholestyramine forms a non-absorbable complex with many drugs, sequestering the drugs within the complex and preventing absorption of the drugs from the GI tract.



https://www.semanticscholar.org/paper/Interactions-with-the-Absorption-of-Tetracyclines-Neuvonen/a7e7a9648720532ba8563fc5a1bfcb488c299096

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Questions: You are invited to pause the video to answer them.

- **What is the difference between two-state receptor occupancy model and the classical receptor occupancy model explaining drug-receptor interactions?**

- **How are antagonists classified and what are the effects on agonist's efficacy?**

Receptor Dynamics:

- Cellular regulation of drug-receptor interactions prevents overstimulation that can harm the cell or the entire organism.
- As a result of this physiologic regulation, many drugs show diminishing effects over time.

Receptor Dynamics: Terms

Diminished response (tolerance) due to exposure to an agonist:

- **Receptor desensitization:** A decrease in the coupling efficiency of receptors – the receptor and the cell become unresponsive (insensitive) to the action of the drug, even in the continued presence of the drug.
- **Receptor downregulation:** A decrease in the number of receptors by internalization followed by degradation of the receptor (and ligand)

When the rate of receptor degradation is faster than de novo receptor synthesis, fewer receptors are present on the cell surface and responsiveness to the agonist is diminished.

- **Tachyphylaxis:** An acute, sudden decrease in response after continuous or repeated administration of a drug
- **Receptor resensitization:** After withdrawal of the agonist, cells recover full responsiveness to a subsequent addition of the agonist.

Enhanced response / increased sensitivity due to exposure to an antagonist:

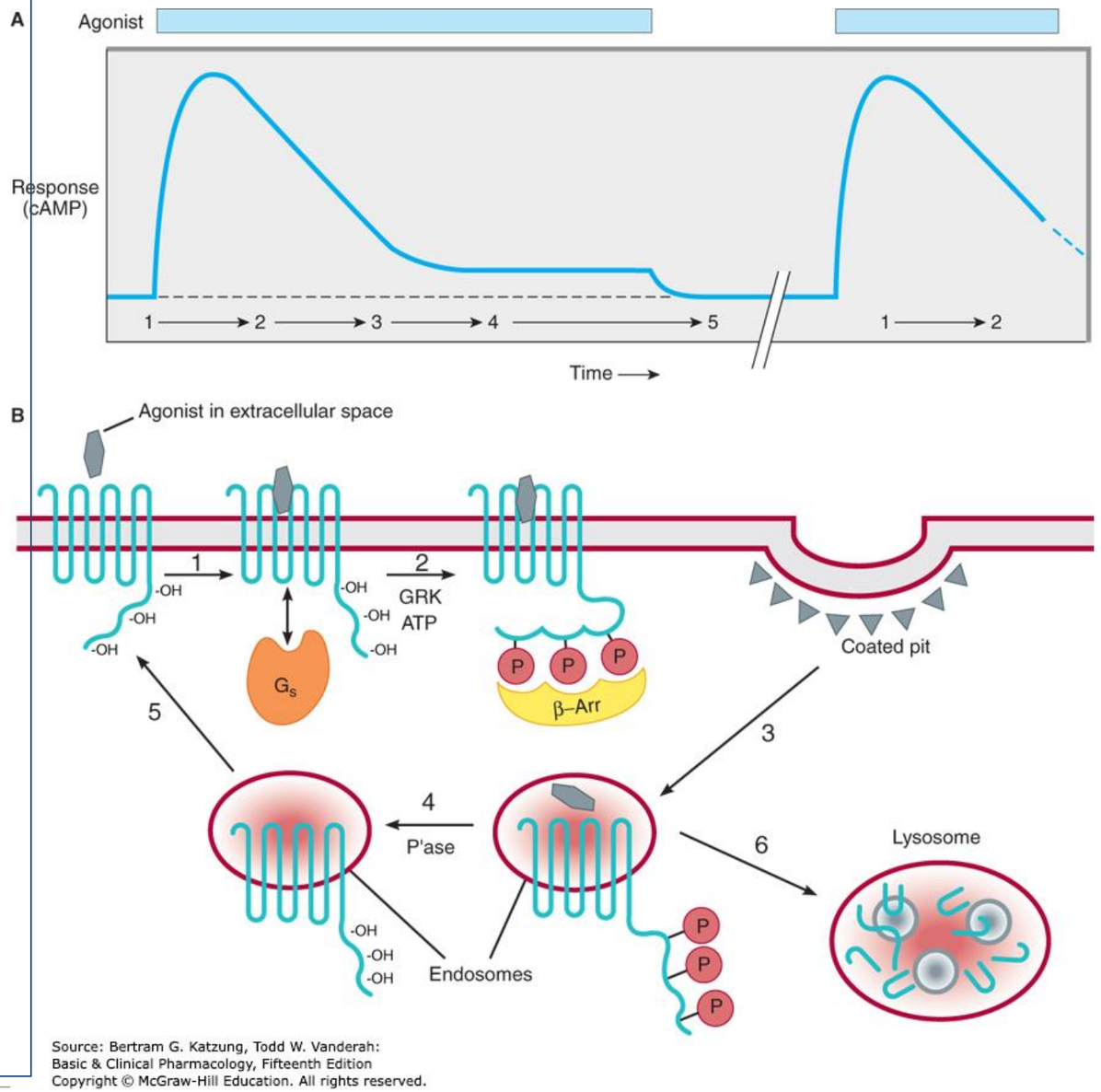
- Supersensitivity: Insertion of an increased number of receptors on the membrane can make cells more sensitive to an agonist

Panel A: Response to a beta-adrenoceptor agonist *vs* time
Resensitization: The cell recovers its capacity to respond when the agonist is removed for a short time.
Note: Resensitization is reduced or absent if cells are exposed to agonist repeatedly or over a more prolonged time.

Panel B

1. Agonist binding → signaling initiated
2. Phosphorylation by a GPCR kinase (GRK) and binding of arrestin (-Arr) → prevents R interaction with G protein
3. R-arrestin complex binds to coated pits → receptor internalization
4. Agonist dissociates from internalized receptors →→ receptor dephosphorylation
5. Receptors are returned to the plasma membrane → resensitization of cellular responsiveness
6. Receptors are internalized in lysosomes (receptor downregulation) is favored by repeated or prolonged exposure of cells to agonist

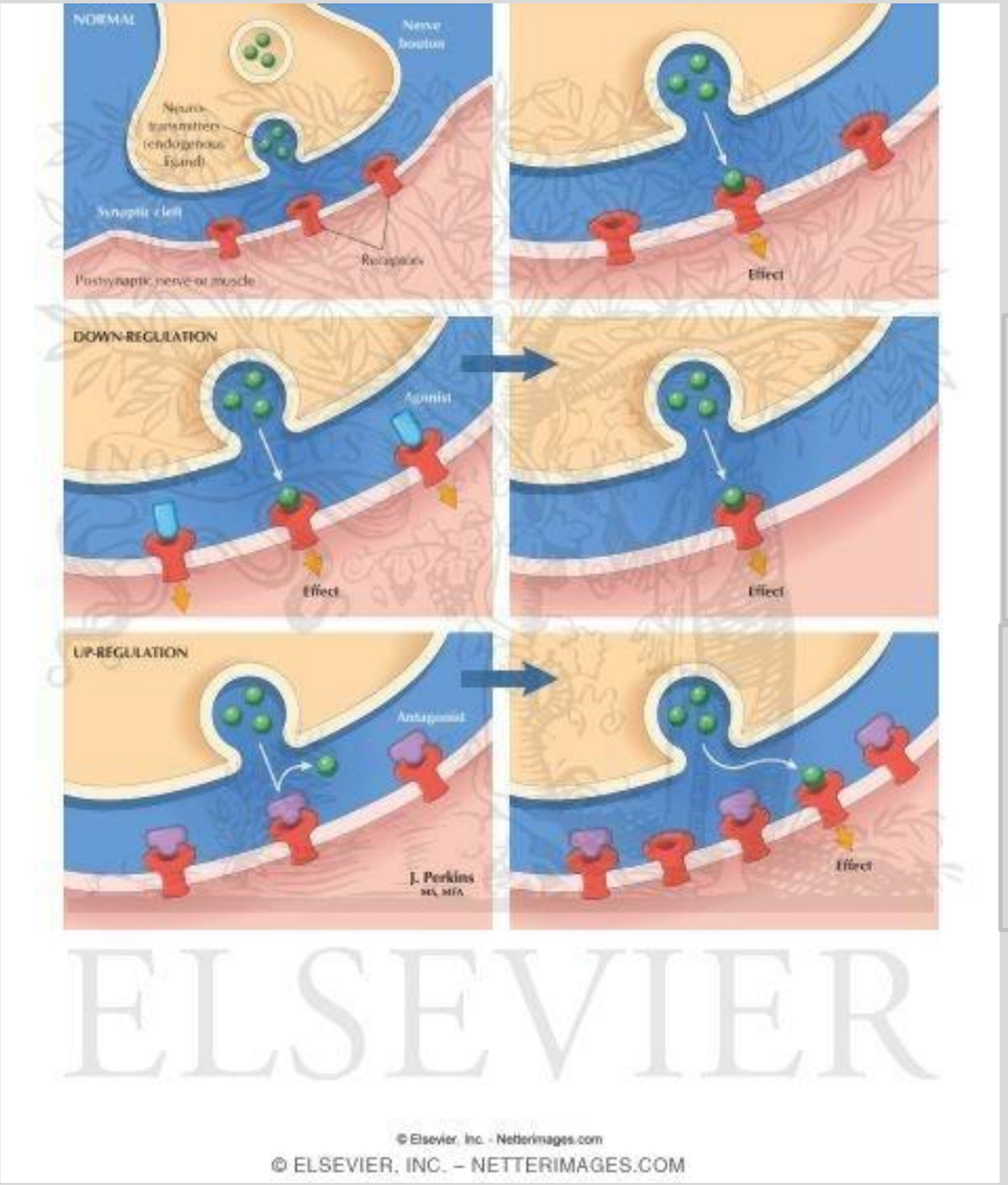
Adrenoceptor desensitization, resensitization and downregulation of β adrenergic receptors



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

Citation: Chapter 2 Drug Receptors & Pharmacodynamics, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250594122 Accessed: June 22, 2021

Slide adapted by LG



http://www.netterimages.com/image/5037.htm

NORMAL

Receptor downregulation with exposure to an agonist:

Internalization and degradation can lead to reduced receptors on cell surface and diminished response.

Receptor upregulation with exposure to an antagonist:

Increased expression of receptors on cell surface can lead to an exaggerated response (supersensitivity) after the **antagonist** is withdrawn.

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Questions: You are invited to pause the computer.

- **How does receptor desensitization and downregulation affect response to a natural or drug agonist?**

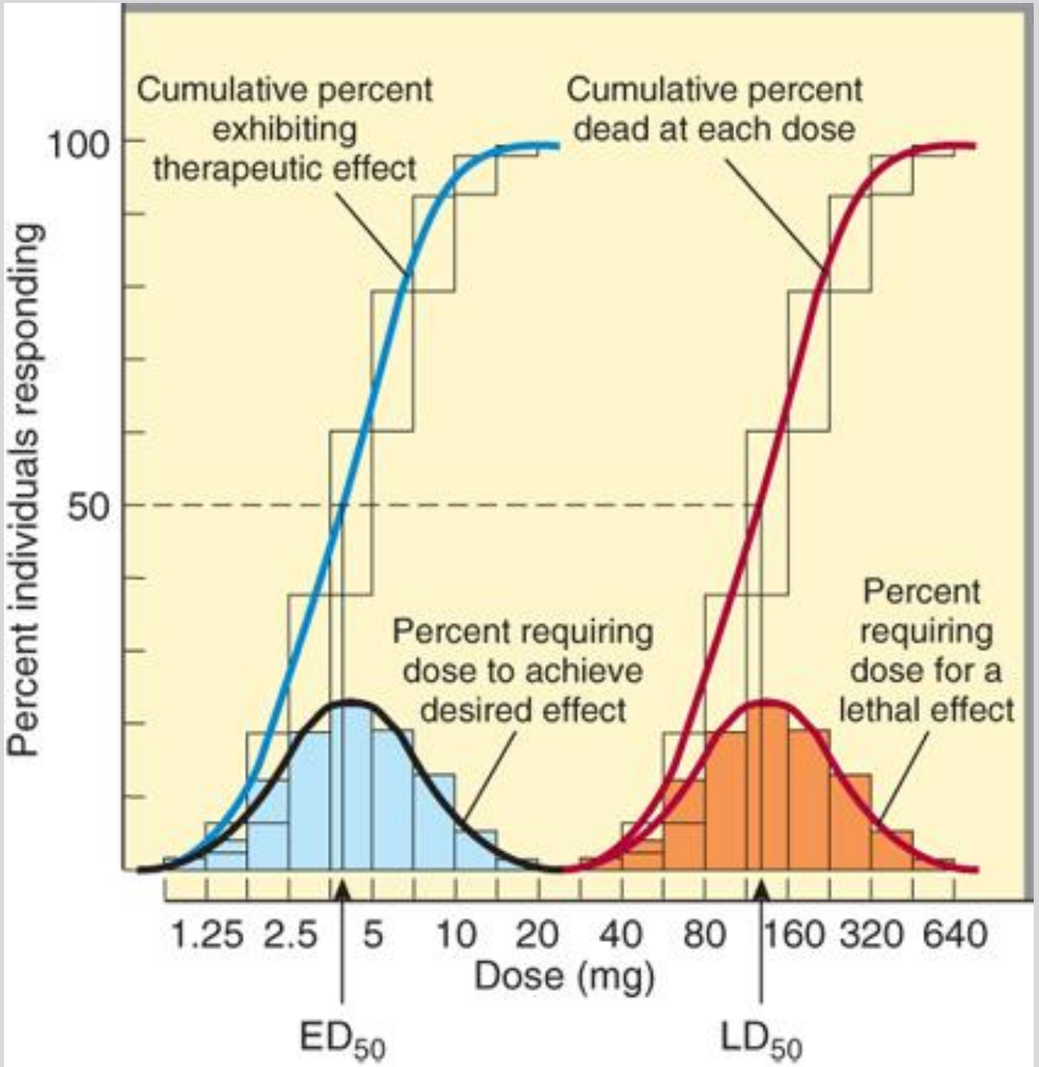
- **How does receptor supersensitivity affect response to a natural or drug agonist?**

Pharmacodynamic variability in a population

The response to a drug – the effect – is specified to be either present or absent in a given individual – an either-or (quantal) event.

Determining the dose of a drug required to produce a specified effect in a large number of individual patients or experimental animals and plotting quantal dose-response can be used to generate information on the margin of safety to be expected for a particular drug.

- In a population, there is usually some variation in the dose needed to achieve a specified drug effect.
- The response elicited with each dose is plotted against the log dose of the drug.
- The percentage of the population affected increases as the dose is raised.



Source: Todd W. Vanderah:
Basic & Clinical Pharmacology, Sixteenth Edition

Citation: Chapter 2 Drug Receptors & Pharmacodynamics, Todd W. Vanderah. *Katzung's Basic & Clinical Pharmacology, 16th Edition;* 2024. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3382&sectionid=281746891

Therapeutic index (TI) is an *estimate* of the safety of a drug.

- **Median effective dose (ED_{50}):** The dose of a drug required to produce a specified effect in 50% of the population.
- **Median lethal dose (LD_{50}):** The dose of a drug that is lethal in 50% of the population.
- **Median toxic dose (TD_{50}):** The dose of a drug that produces a specified toxic effect in 50% of the population.

The therapeutic index relates the dose of a drug required to produce a desired effect to the dose that produces an undesired effect.

LD_{50} and TD_{50} are experimentally defined.

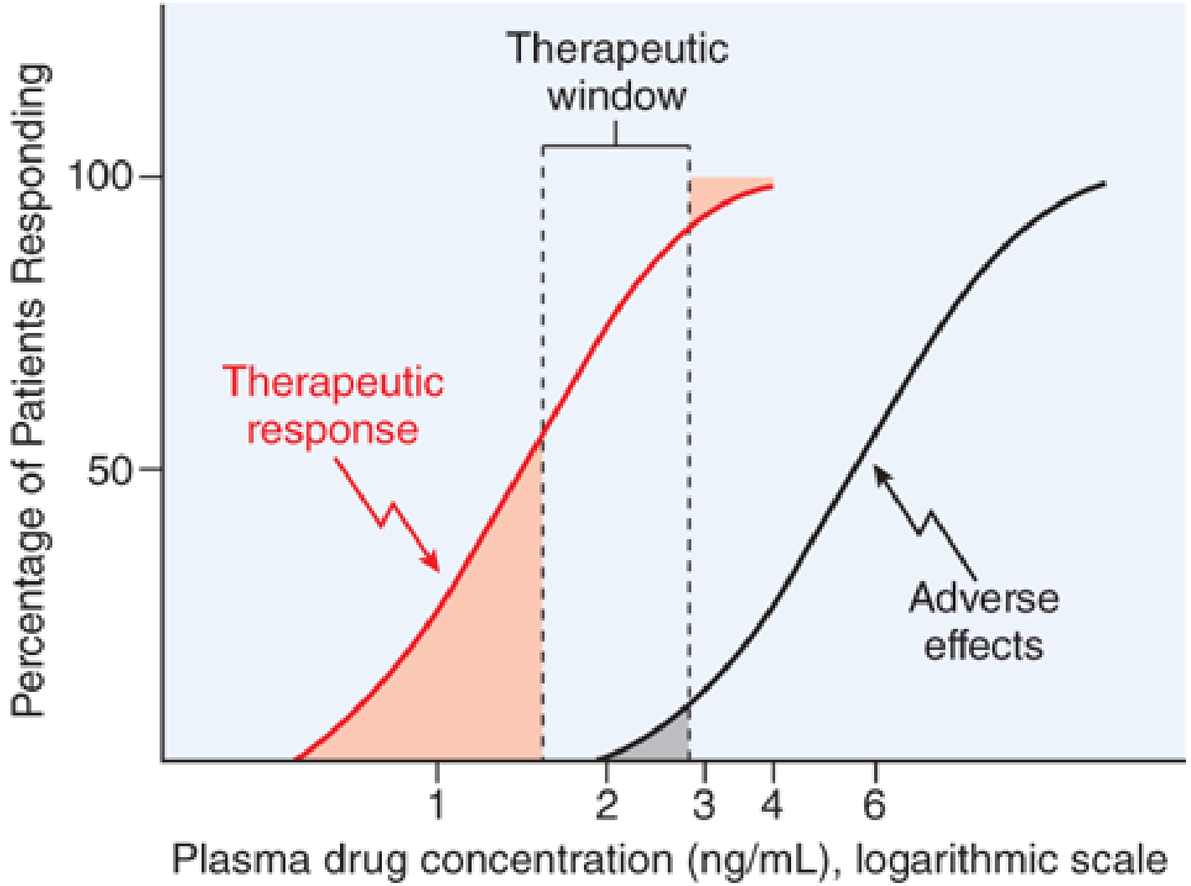
$$\mathbf{TI = LD_{50}/ED_{50}}$$

$$\mathbf{TI = TD_{50}/ED_{50}}$$

A large TI indicates a wide margin between effective doses and toxic doses.

A small TI indicates a narrow margin. Small changes in systemic concentration can lead to significant drug-related adverse effects.

27



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:

The therapeutic window represents the range of steady state concentrations (dose range) at which the:

- likelihood of efficacy is high,

and the

- probability of adverse effects is low.

This range does not guarantee safety or efficacy in individual patients.

Relation of the therapeutic window of drug concentrations to therapeutic and adverse effects in the population. The ordinate is linear; the abscissa is logarithmic. This particular therapeutic window represents the difference in drug concentrations eliciting a therapeutic response in 50% of the patients and adverse effects in 10%.

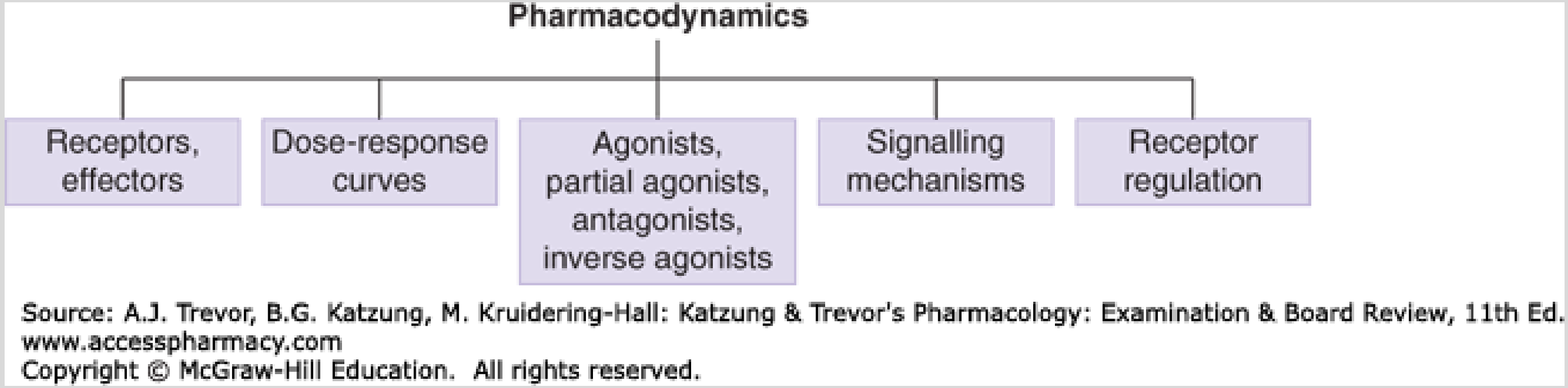
Citation: Chapter 3 Pharmacodynamics: Molecular Mechanisms of Drug Action, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e;* 2023, Figure 3-10. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=269715460 Accessed: June 06, 2023

Question: You are invited to pause your computer.

- **What is the clinical value of the therapeutic index and therapeutic window?**

SUMMARY OF PHARMACODYNAMICS PART 2

Pharmacodynamics is the study of the effects of drugs on biologic systems.



Katzung & Trevor's Pharmacology: Examination & Board Review, 11e, 2015
Chapter 2: Pharmacodynamics

- The two-state receptor occupancy model postulates that receptors in the receptor pool exist in equilibrium in two interchangeable conformational states in the absence of a ligand: R_a (active) and R_i (inactive). Full agonists, partial agonists, neutral antagonists, and inverse agonists are explained by this model.
- The classical receptor occupancy model postulates that receptors are quiescent unless activated by a ligand. Agonists occupy receptors activate their regulatory effector mechanisms producing a response – agonists have affinity and intrinsic activity. Antagonists occupy receptors and do not activate them – they have affinity, zero intrinsic activity, and prevent the agonist from occupying the site of action.
- Receptor antagonists are classified as competitive and noncompetitive antagonists, irreversible and allosteric modulators. Positive allosteric modulators increase agonist affinity or magnitude of effect. Negative allosteric modulators reduce affinity and/or efficacy of the agonist.
- Physiologic (functional) antagonism results from counterbalancing effects on physiological regulatory pathways by substances acting at different receptors. Chemical antagonists sequester the agonist, preventing it from binding its receptors.

- Cellular regulation of drug-receptor interactions can alter the response to the agonist over time. Diminished responsiveness (tolerance/tachyphylaxis) due to continuous or repeated exposure to an agonist results from receptor desensitization and downregulation. After withdrawal of the agonist, the cells recover full responsiveness to a subsequent addition of agonist (resensitization).
- An increased density of membrane receptors – receptor supersensitivity – can result from continuous or repeated exposure to an antagonist. After the antagonist is withdrawn, activation by the agonist can cause an exaggerated response.
- Individuals in a population vary in their response to the same concentration of a single drug or to similar drugs, and a given individual may not always respond in the same way to the same drug concentration.
- Quantal dose-response curves describe the cumulative frequency distributions of responders defined as an all-or-none effect plotted against the log dose of a drug. The percentage of the population affected increases as the dose is raised.
- The parameters for calculating the therapeutic index (TI) are the dose of drug required to produce an effect in 50% of the population (ED_{50}) and the dose that produces death (LD_{50}) or toxicity (TD_{50}) in 50% of the population. The TI is an estimate of a drug's safety.
- The therapeutic window is the range of steady state concentrations at which the likelihood of efficacy is high and the probability of adverse effects is low.

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Answers to the Questions:

What is the difference between two-state receptor occupancy model and the classical receptor occupancy model explaining drug-receptor interactions?

- The two-state receptor occupancy model posits that receptors in the receptor pool exist in an inactive and an active conformation in the absence of ligand with equilibrium favoring the inactive state. Drug binding to receptors shifts the equilibrium depending on the drug's relative affinities for the active and inactive states.

How are antagonists classified and what are the effects on agonist's efficacy?

- The classical model posits that receptors in a receptor pool are quiescent unless activated by a ligand. Agonists have affinity for receptors and activate the receptors' effector pathways. Antagonists have affinity for receptors but do not activate the receptors and they prevent the agonist from activating the receptors.
- Competitive antagonists compete for the same binding site as the agonist and affect the amount of agonist needed to achieve a maximal response.
- Noncompetitive antagonists reduce the magnitude of the maximal response that can be achieved by any amount of agonist without having an effect on the binding of the agonist to the receptor.

Answers to the Questions

How does receptor desensitization and downregulation affect response to a natural or drug agonist?

- Diminished response to continuous or repeated exposure to an agonist can lead to fewer receptors or desensitized receptors on the cell surface. After withdrawal of the agonist, cells recover full responsiveness to a subsequent addition of the agonist (resensitization).

How does receptor supersensitivity affect response to a natural or drug agonist?

- Continuous or repeated exposure to an antagonist can cause upregulation of receptors and insertion of an increased number of receptors on cell surfaces. After the antagonist is withdrawn, the increased receptor density can result in an exaggerated response to a natural or drug agonist agonist – supersensitivity.

Answer to the Question

- **What is the clinical value of the therapeutic index and therapeutic window?**
- The therapeutic index relates the dose of a drug required to produce a desired effect to the dose that produces an undesired effect. It is an ***estimate*** of the safety of a drug.
- The therapeutic window is the dosage range of a drug that provides safe and effective therapy with minimal adverse effects.

🔔 ***This range does not guarantee safety or efficacy in individual patients.***

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