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

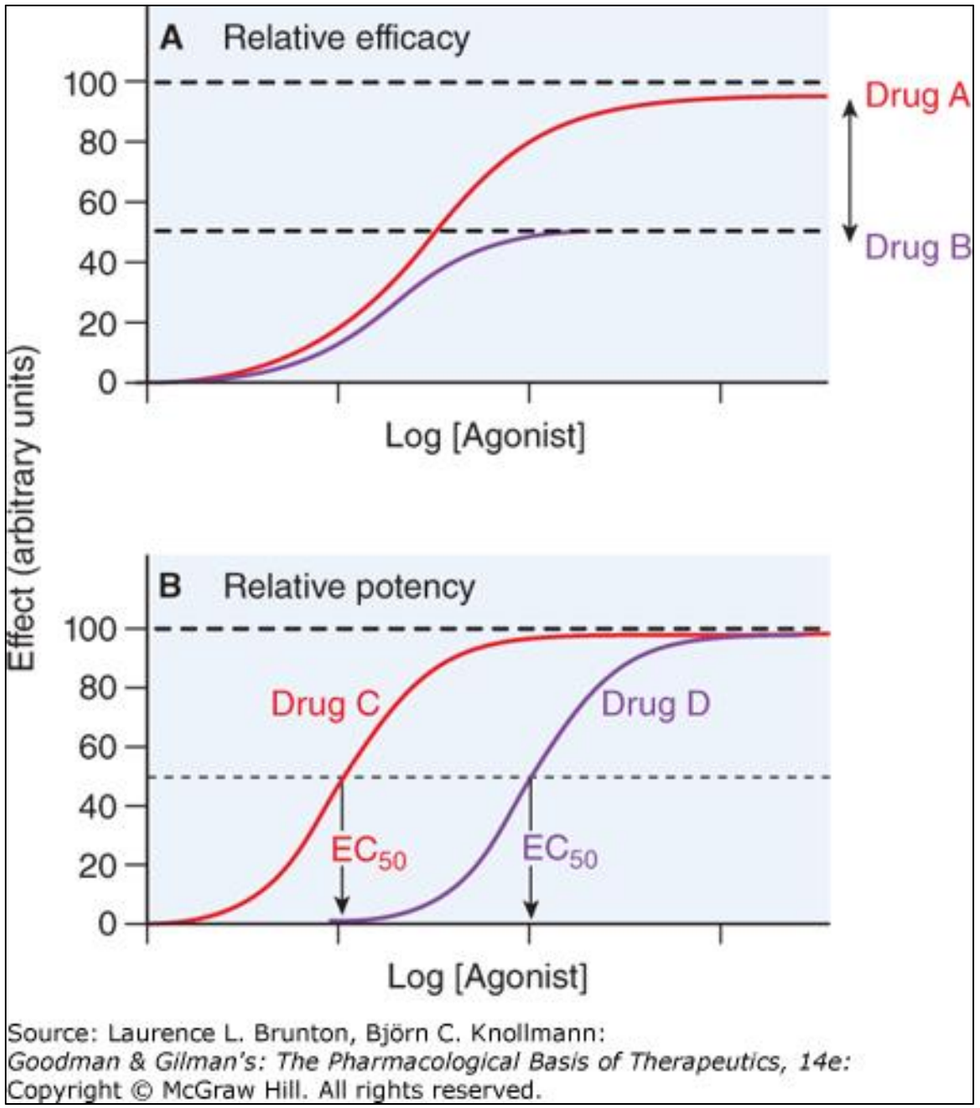
Dose-Concentration-Effect
relationship

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

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.

Relative Efficacy and Relative Potency

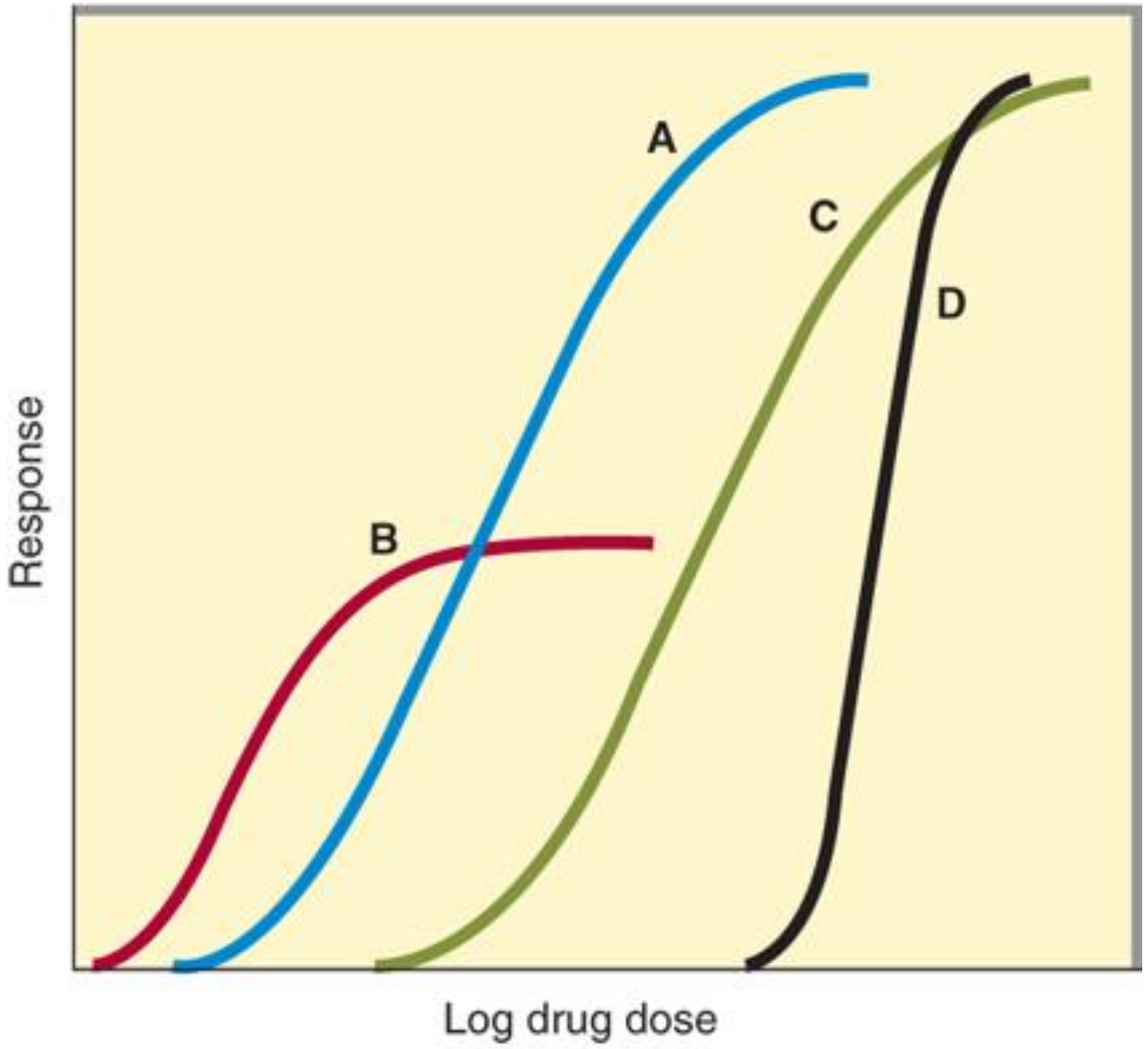


- **Efficacy:** The observed maximal responses of Drug A and Drug B binding to the same receptor is a function of their relative intrinsic activity (efficacy)
  - **the drug with greater efficacy produces a greater magnitude of effect than the drug with lesser efficacy**
- **Potency:** The relative potency 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.

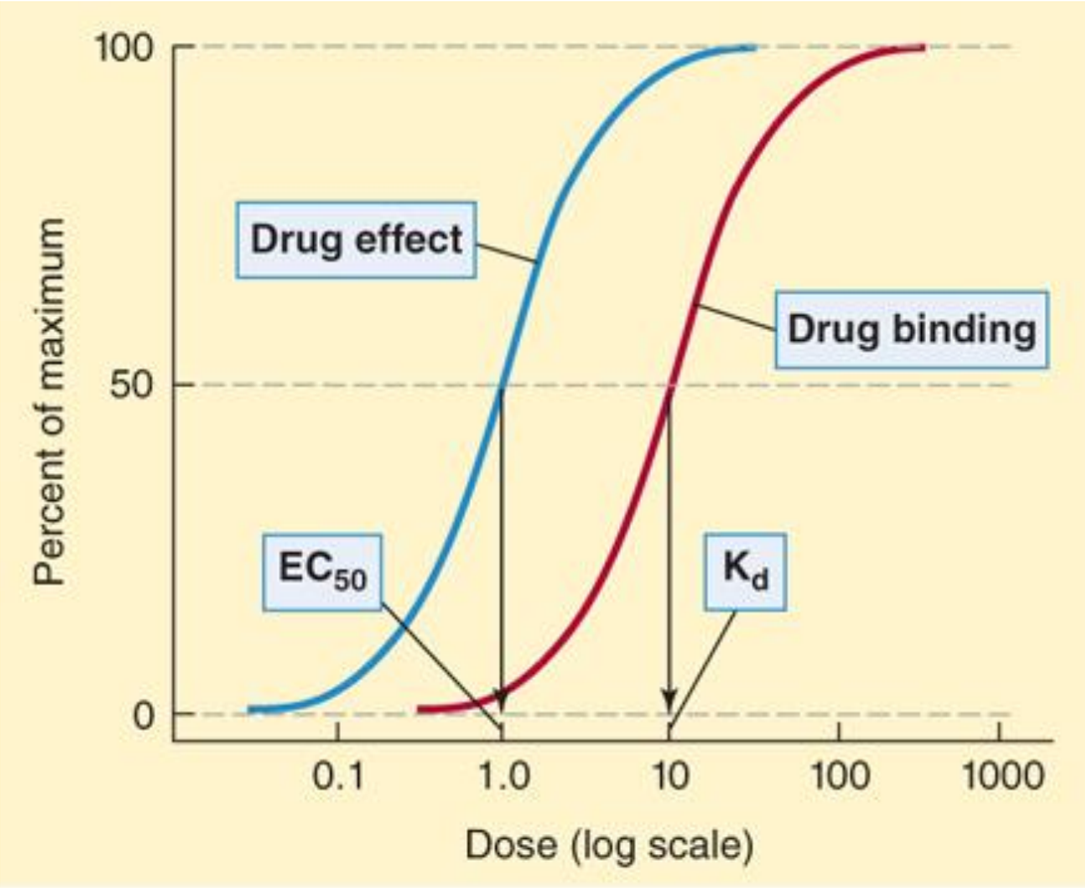
Citation: Chapter 2 Drug Receptors & Pharmacodynamics, Todd W. Vanderah. *Katzung's Basic & Clinical Pharmacology, 16th Edition;* 2024, Figure 2-15.
Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3382&sectionid=281746891

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,

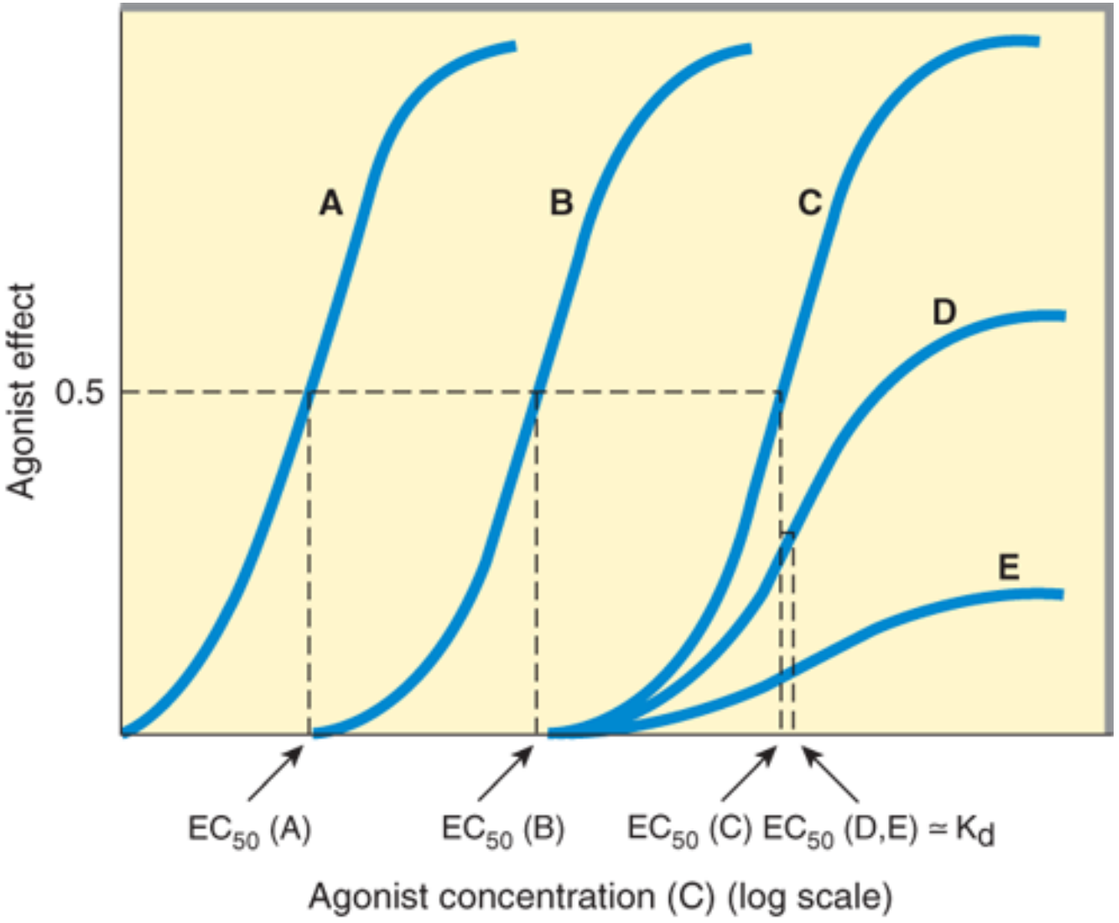
- **The remaining receptors that are not bound by agonist are referred to as spare receptors.**

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

Slide adapted by LG

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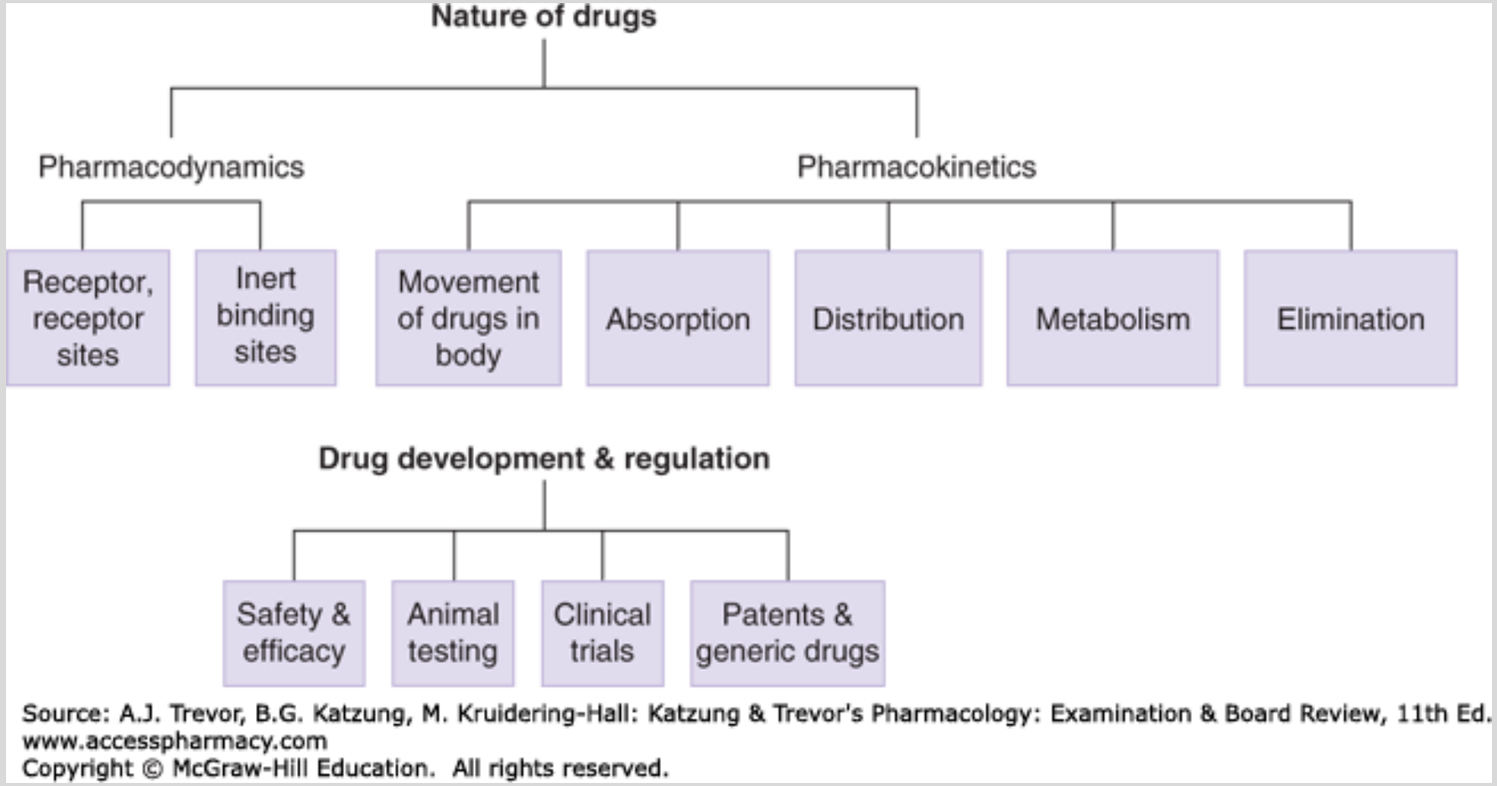
1. Pharmacodynamics is the study of the biochemical, cellular, and physiologic effects of drugs and their mechanisms of action. “What the drug does to the body, and how it does it.”
2. Pharmacokinetics is the study of the movement and fate of drugs in the body: absorption, distribution, metabolism, and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

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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 propose explanations of the activity of drugs at receptors.

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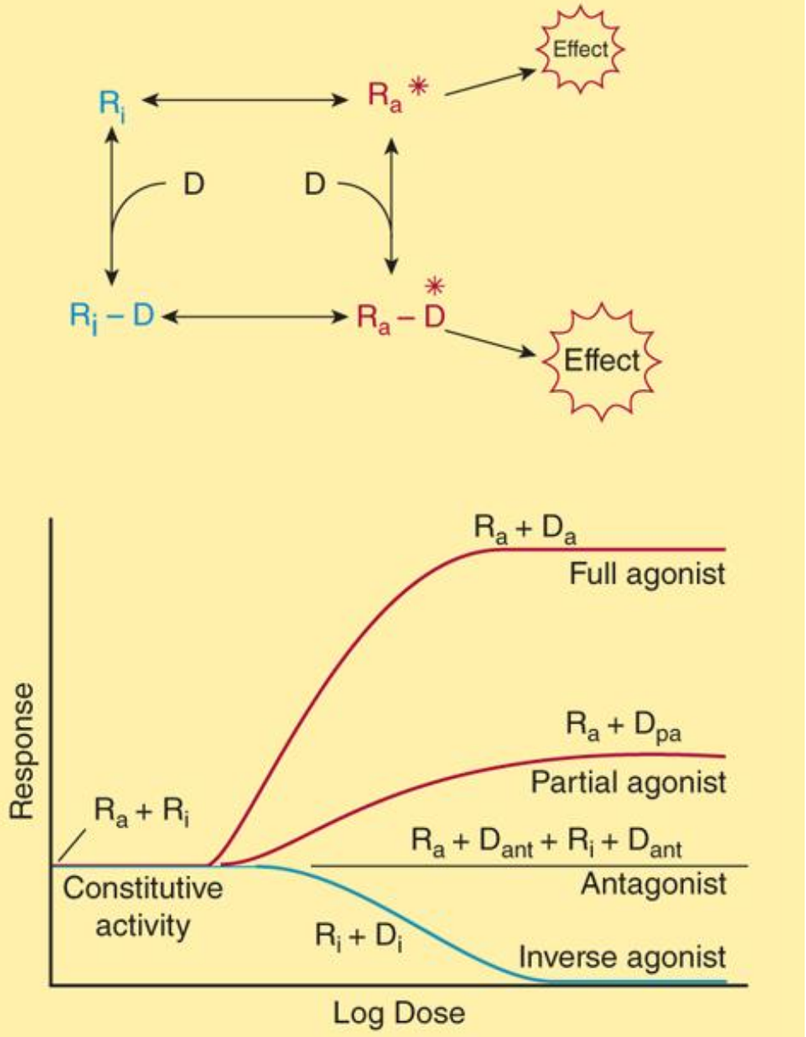
Two-State Receptor Occupancy Model postulates that the receptor assumes two conformational states – active and inactive – in the absence of a ligand.	**Classical receptor occupancy model** postulates that receptors in a receptor pool are quiescent unless activated by a ligand.
Even in the absence of 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.

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.

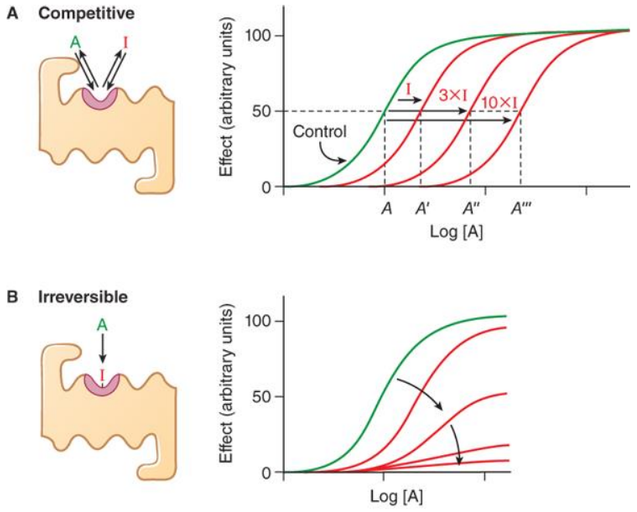
(Panel B, upper: As antagonist concentration increases, the agonist's dose-response curves shift rightward and downward, suggesting some degree of spare receptors.)

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.

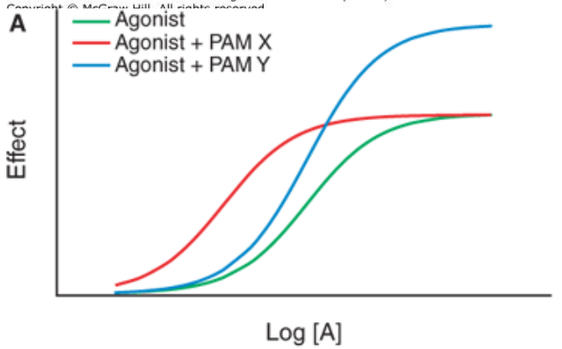
(Panel A, lower: PAM X, shifts the agonist's EC_{50} leftward, which increases the affinity/potency of the agonist. PAM Y increases the E_{max} for the agonist.)

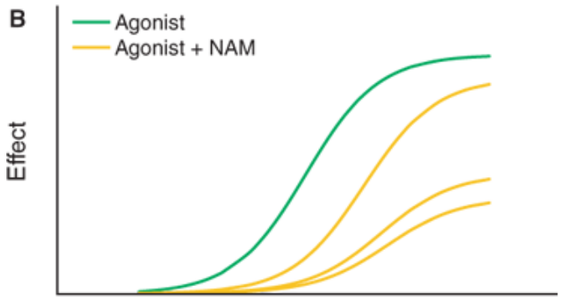
Negative allosteric modulator: A drug that binds to a site on the receptor other than the active site and reduces the affinity and/or the efficacy of the agonist. The EC50 may not be changed.

(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

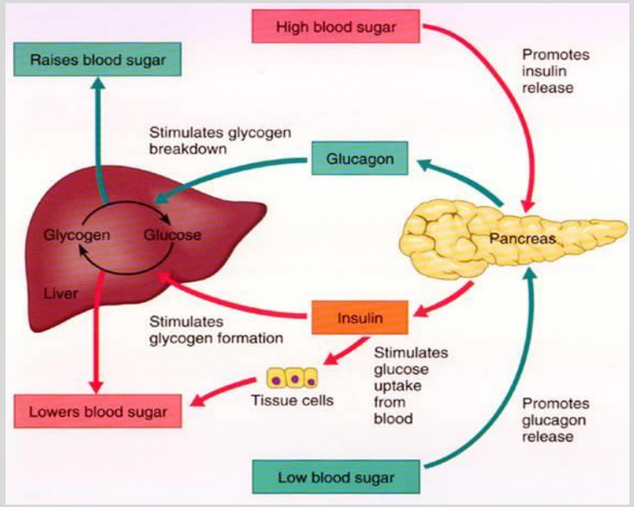
A compound that directly interacts with the agonist, modifying or sequestering it so that the drug is no longer capable of binding to its receptor.

- 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.

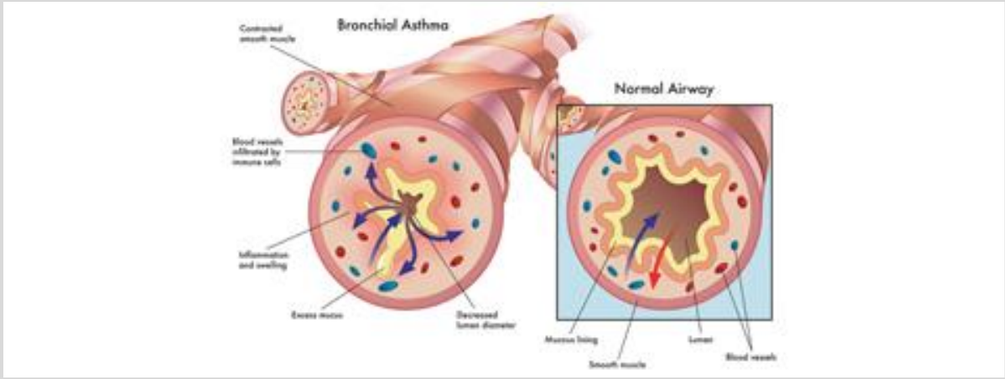
Example: The counterbalancing effects of physiologic (functional) antagonism



- 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.

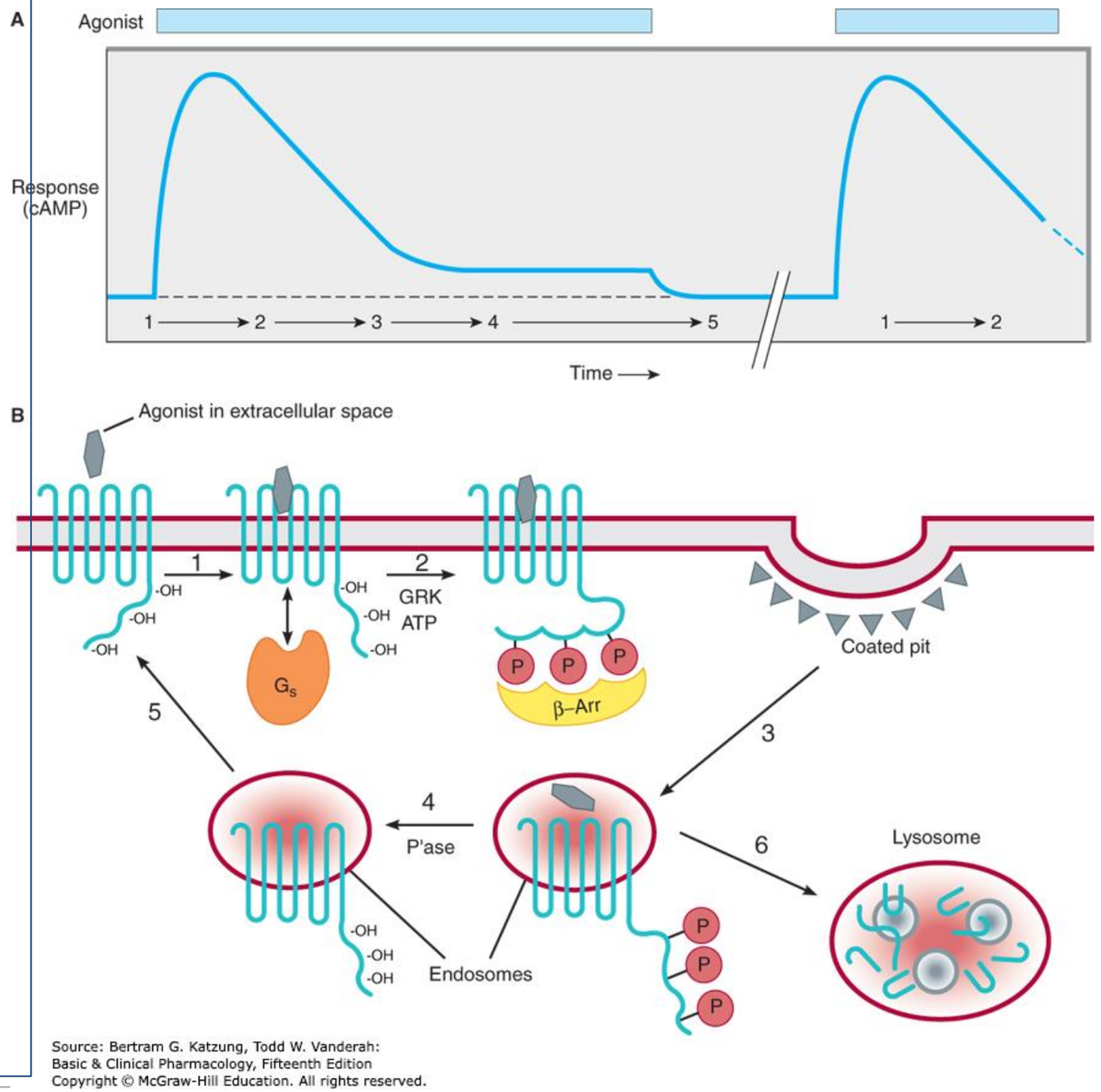
Google images

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

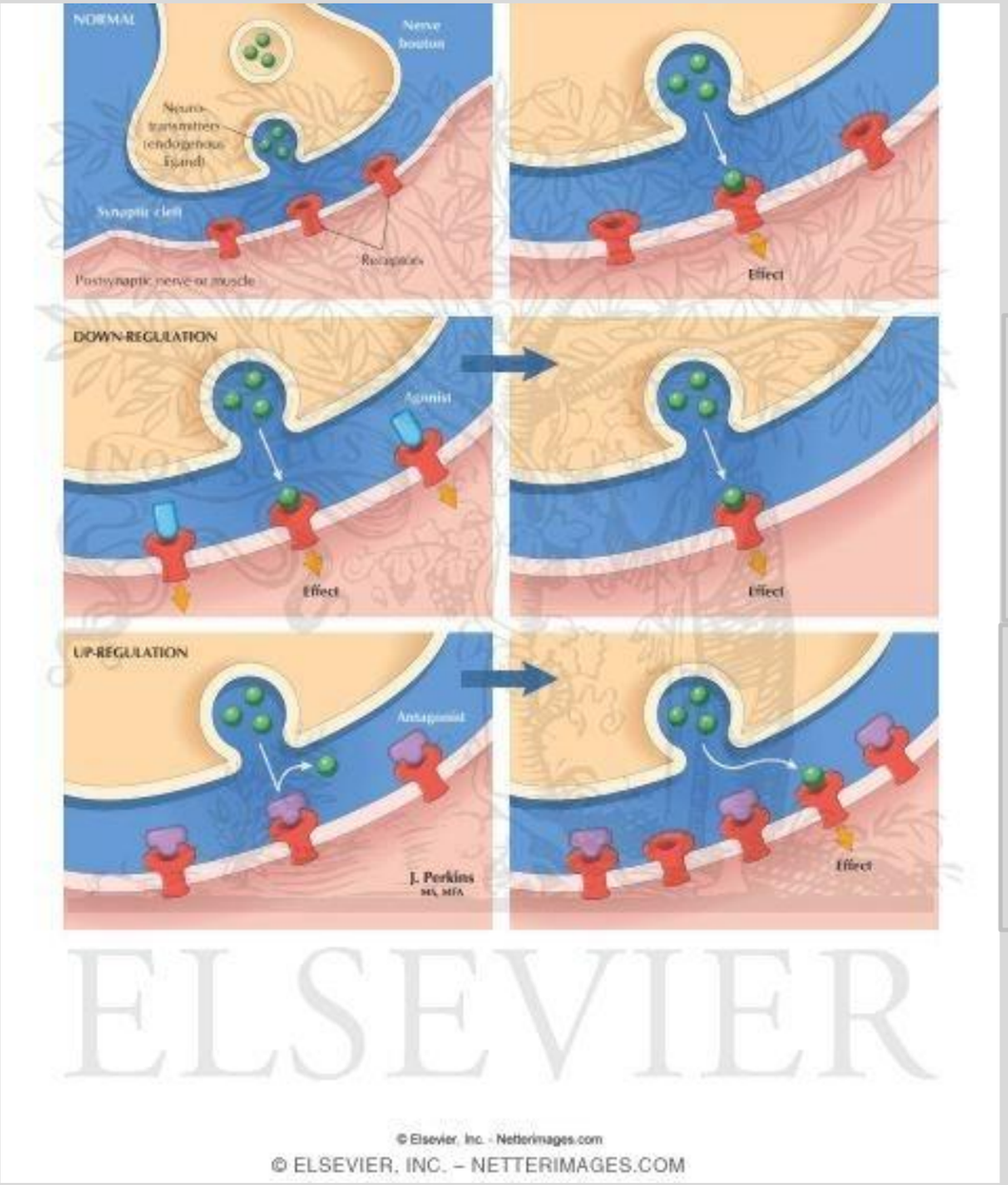
Adrenoceptor desensitization, resensitization and downregulation of β adrenergic receptors



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

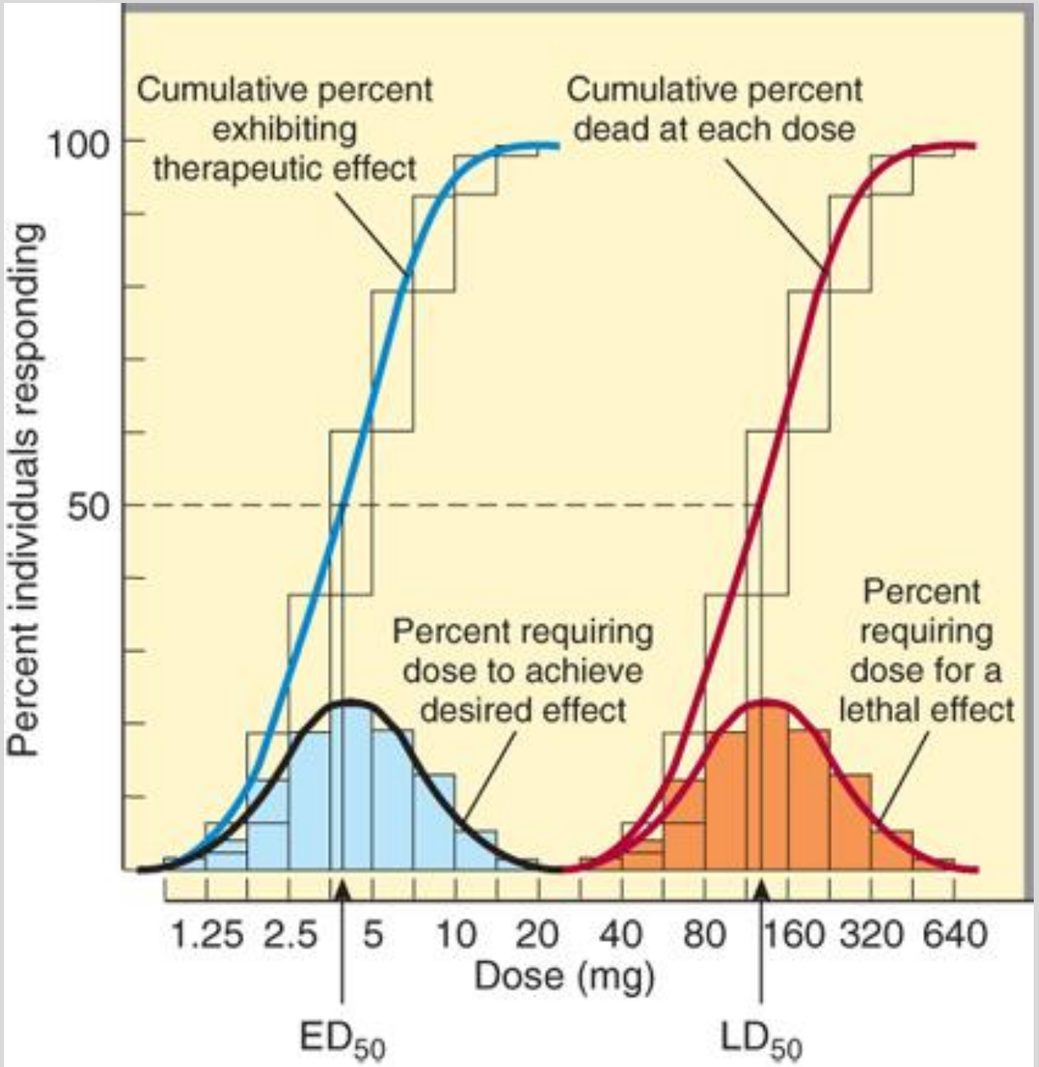
Receptor downregulation with exposure to an agonist:

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.

- 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.

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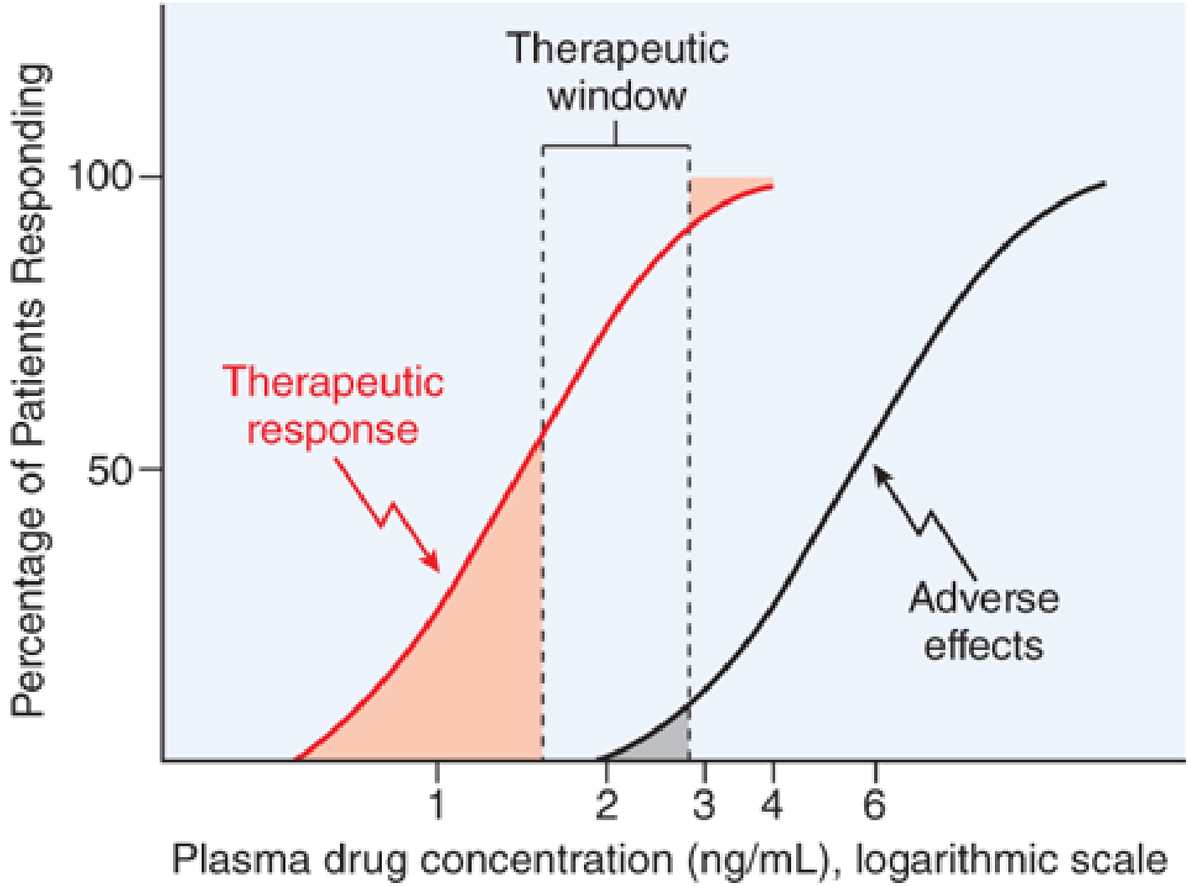


Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:

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%.

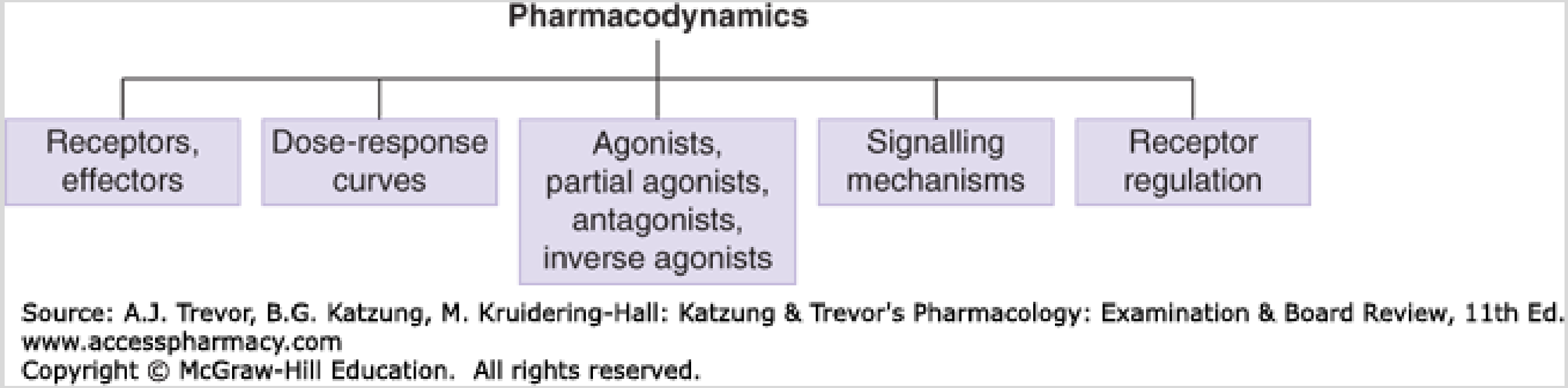
Citation: Chapter 3 Pharmacodynamics: Molecular Mechanisms of Drug Action, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e;* 2023, Figure 3-10. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=269715460 Accessed: June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

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.***