PHARMACOLOGY

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Introduction

Pharmacology:

Is the body of knowledge concerned with the action of chemicals on biologic systems. Medical pharmacology is the area of pharmacology concerned with the use of chemicals in the prevention, diagnosis, and treatment of disease, especially in humans.

Toxicology

Is the area of pharmacology concerned with the undesirable effects of chemicals on biologic systems.

Introduction

Pharmacokinetics:

The actions of the body on the drug, including absorption, distribution, metabolism, and elimination. Elimination of a drug may be achieved by metabolism or by excretion. Bio disposition is a term sometimes used to describe the processes of metabolism and excretion

Pharmacodynamics:

The actions of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic actions.

Introduction

Drug receptors:

The molecular components of the body with which drugs interact to bring about their effects.

The nature of drugs

Drugs in common use include inorganic ions, nonpeptide organic molecules, small peptides and proteins, nucleic acids, lipids, and carbohydrates. Some are found in plants or animals, but many are partially or completely synthetic.

Pharmacodynamics

RECEPTORS:

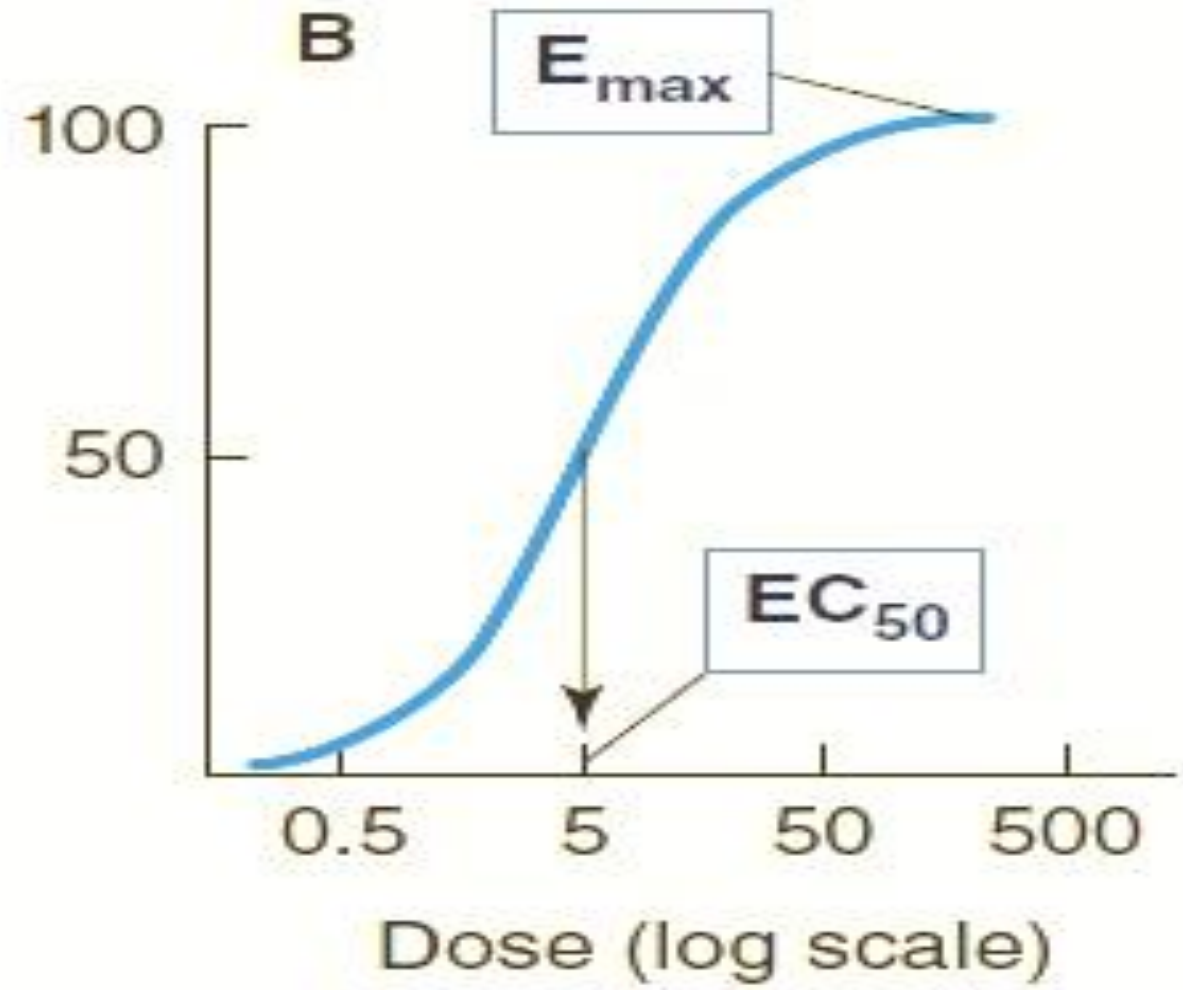
- Receptors are the specific molecules in a biologic system with which drugs interact to produce changes in the function of the system.
- Receptors must be selective in their ligand-binding characteristics.
- Most of receptors are proteins; a few are other macromolecules such as DNA.
- The interaction of a drug with its receptor is the fundamental event that initiates the action of the drug, and many drugs are classified on the basis of their primary receptor affinity

EFFECTORS

- Effectors are molecules that translate the drug–receptor interaction into a change in cellular activity.
- Some receptors are also effectors in that a single molecule may incorporate both the drug-binding site and the effector mechanism.
- For example, a tyrosine kinase effector is part of the insulin receptor molecule.

Pharmacodynamics

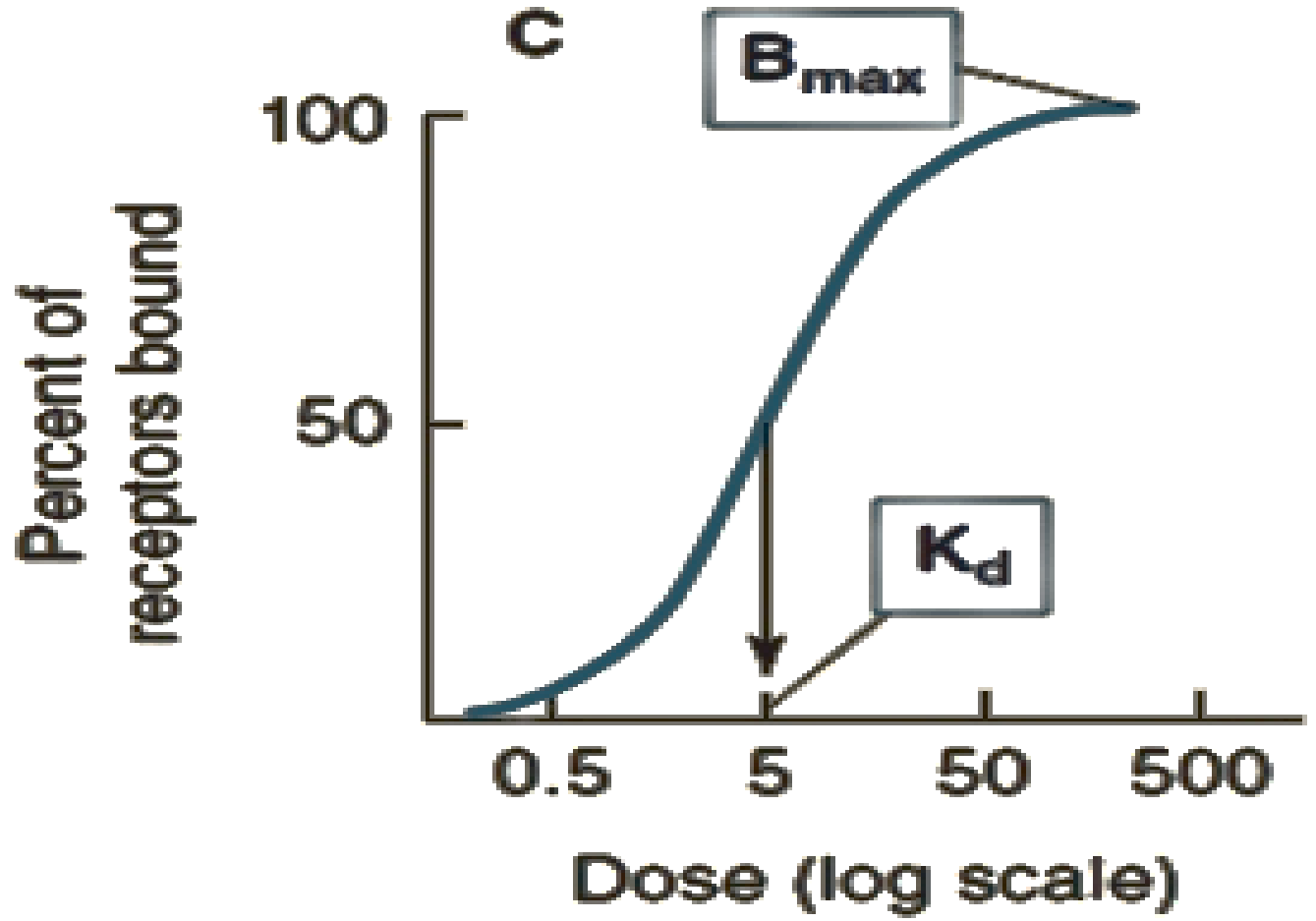
GRADED DOSE–RESPONSE RELATIONSHIPS



GRADED DOSE–BINDING RELATIONSHIP & BINDING AFFINITY

- It is possible to measure the percentage of receptors bound by a drug.
- Kd: The concentration of drug required to bind 50% of the receptor sites and is a useful measure of the affinity of a drug for the receptor molecule.
- The smaller the Kd, the greater the affinity of the drug for its receptor.

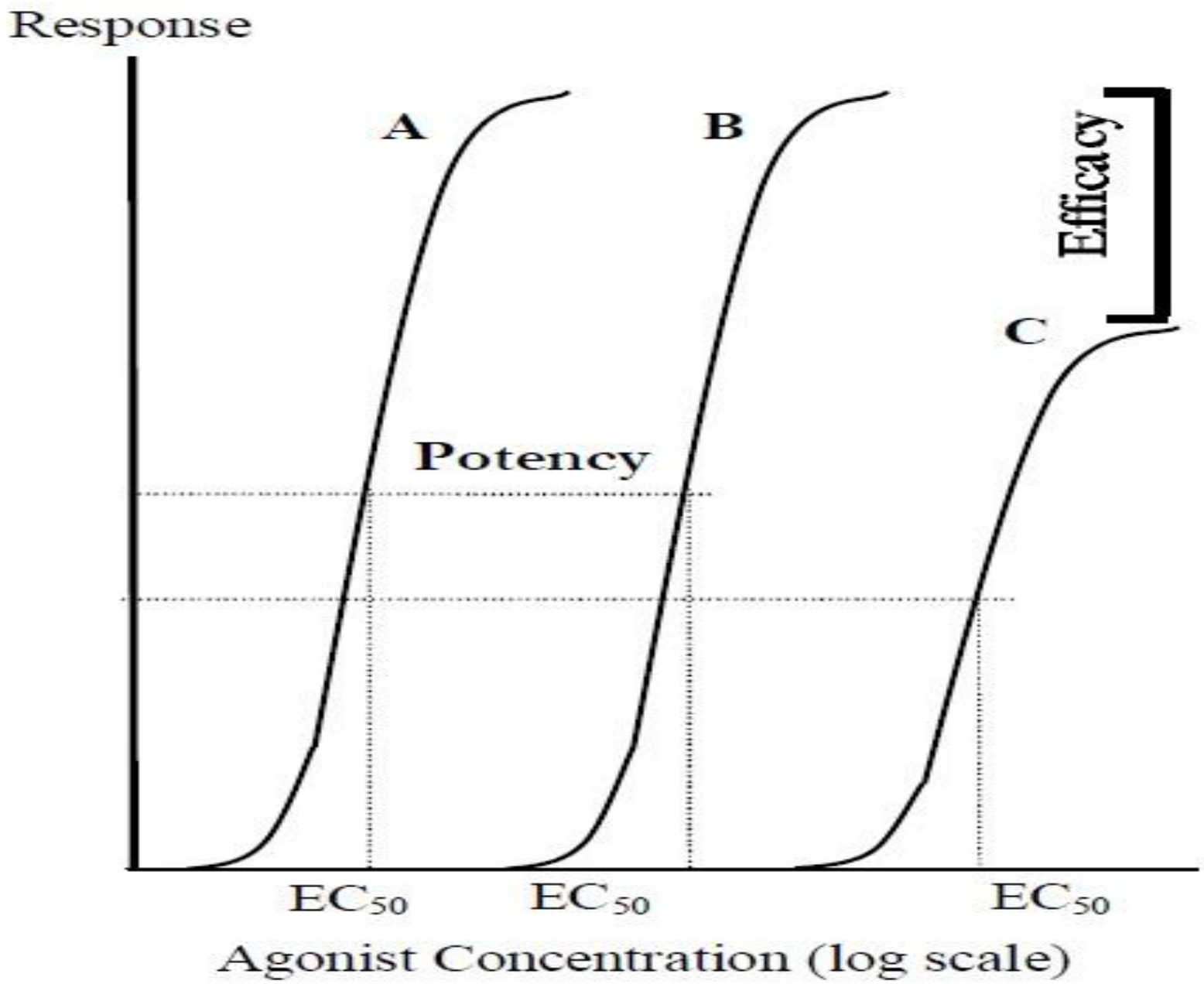
GRADED DOSE–BINDING RELATIONSHIP & BINDING AFFINITY



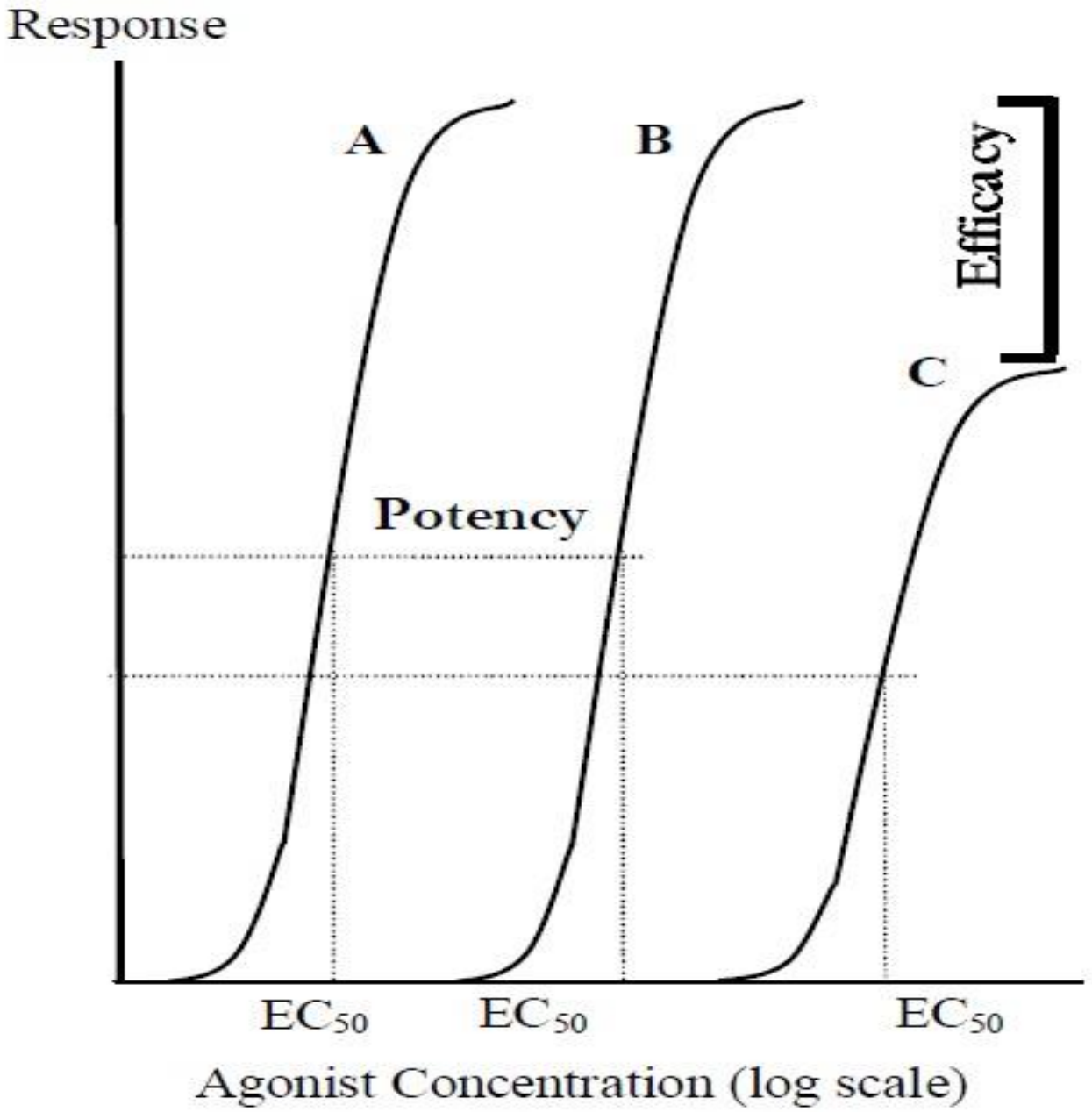
Pharmacodynamics

EFFICACY & POTENCY

Pharmacodynamics



Pharmacodynamics

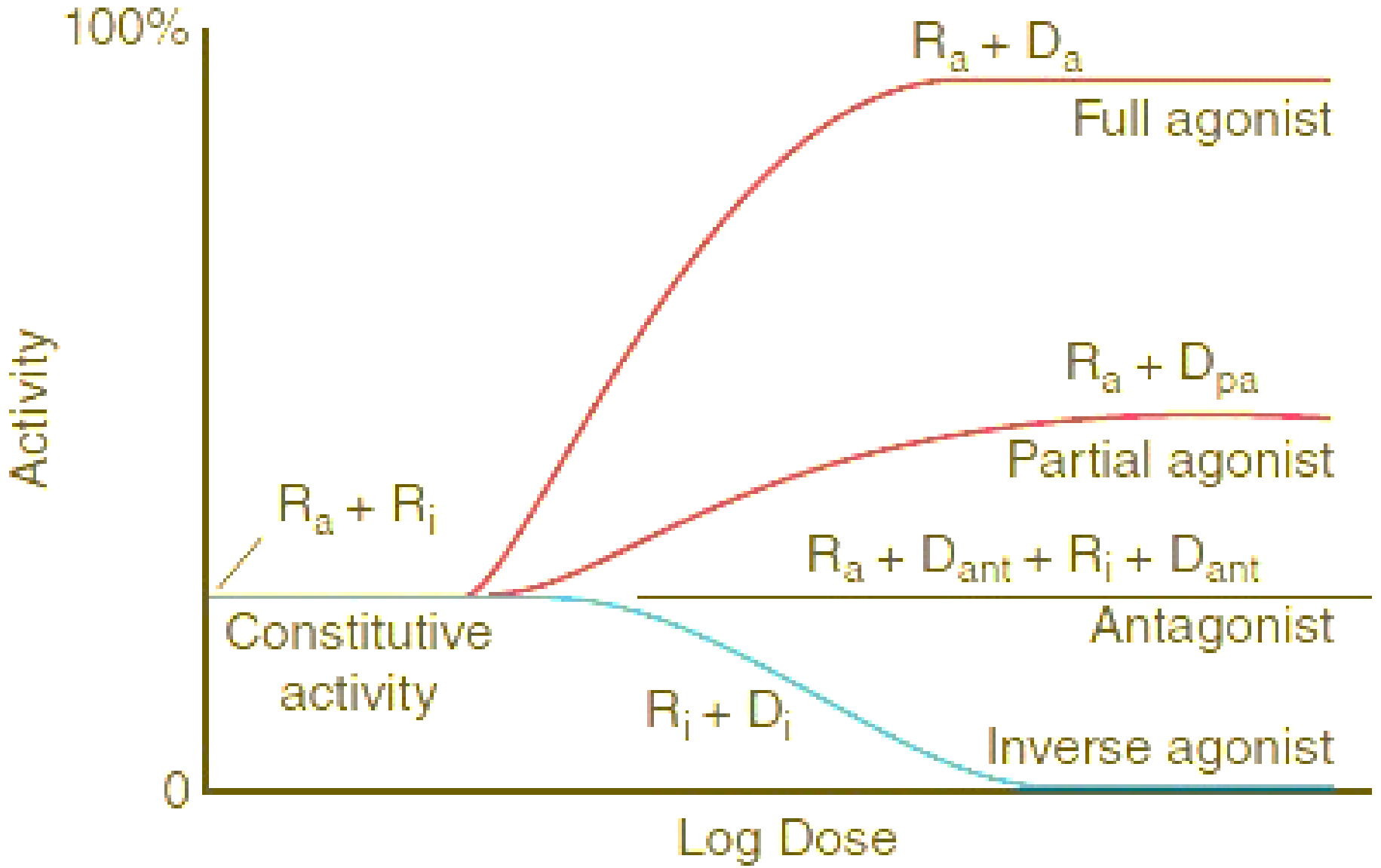


Log dose-response curves for the drugs (A), (B) and (C). Drug (A) is more potent than drug (B) and (B) is more potent than the drug (C), while both A and B are more efficacious (with more efficacy) than C. Note: The maximal response is a measure of the **efficacy** while the EC_{50} is a measure of the **potency**; i.e. a drug with a higher EC_{50} is with a lower potency. When substituting morphine for A, codeine for B and aspirin for C it follows that morphine is more potent than codeine, both are more efficacious and more potent than aspirin as analgesic agents.

Agonists (full agonist & partial agonists)

Modern concepts of drug-receptor interactions consider the receptor to have at least 2 states—active and inactive. In the absence of ligand. Many receptor systems exhibit some activity in the absence of ligand, suggesting that some fraction of the receptors are always in the activated state. Activity in the absence of ligand is called constitutive activity.

Pharmacodynamics



Example

Aripiprazole, an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Dopaminergic pathways that are overactive tend to be inhibited by *aripiprazole,* whereas pathways that are underactive are stimulated. This might explain the ability of *aripiprazole* to improve symptoms of schizophrenia.

Pharmacodynamics

ANTAGONISTS

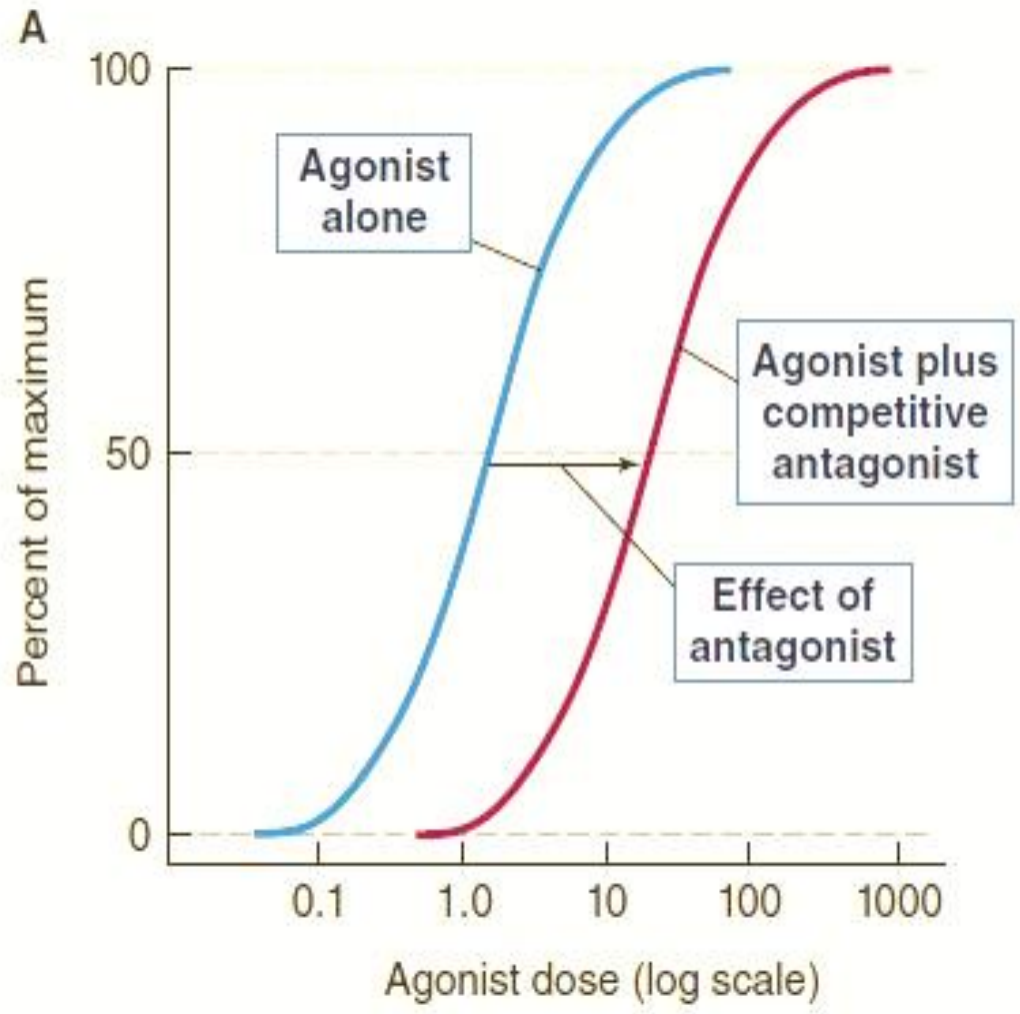
A. Competitive and Irreversible Pharmacologic Antagonists

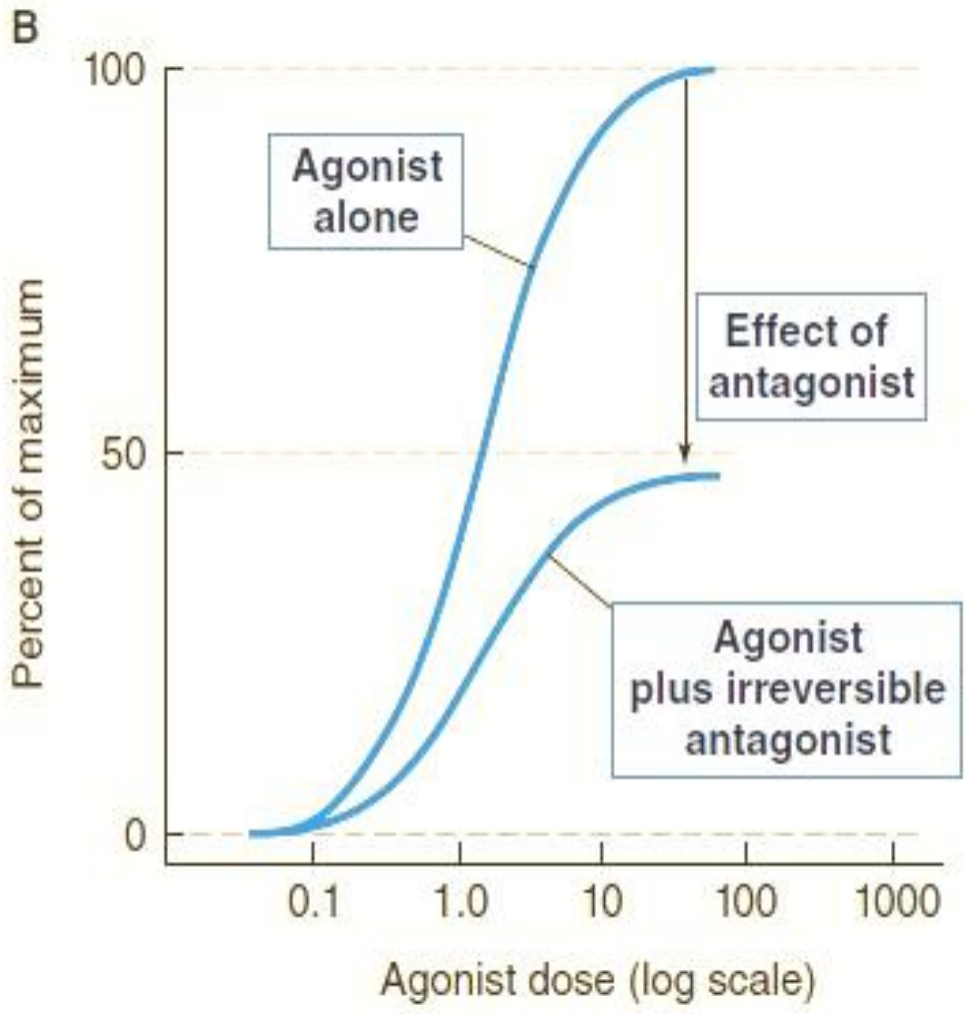
B. Physiologic Antagonists

C. Chemical Antagonists

Pharmacodynamics

A. Competitive and Irreversible Pharmacologic Antagonists





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B. Physiologic Antagonists

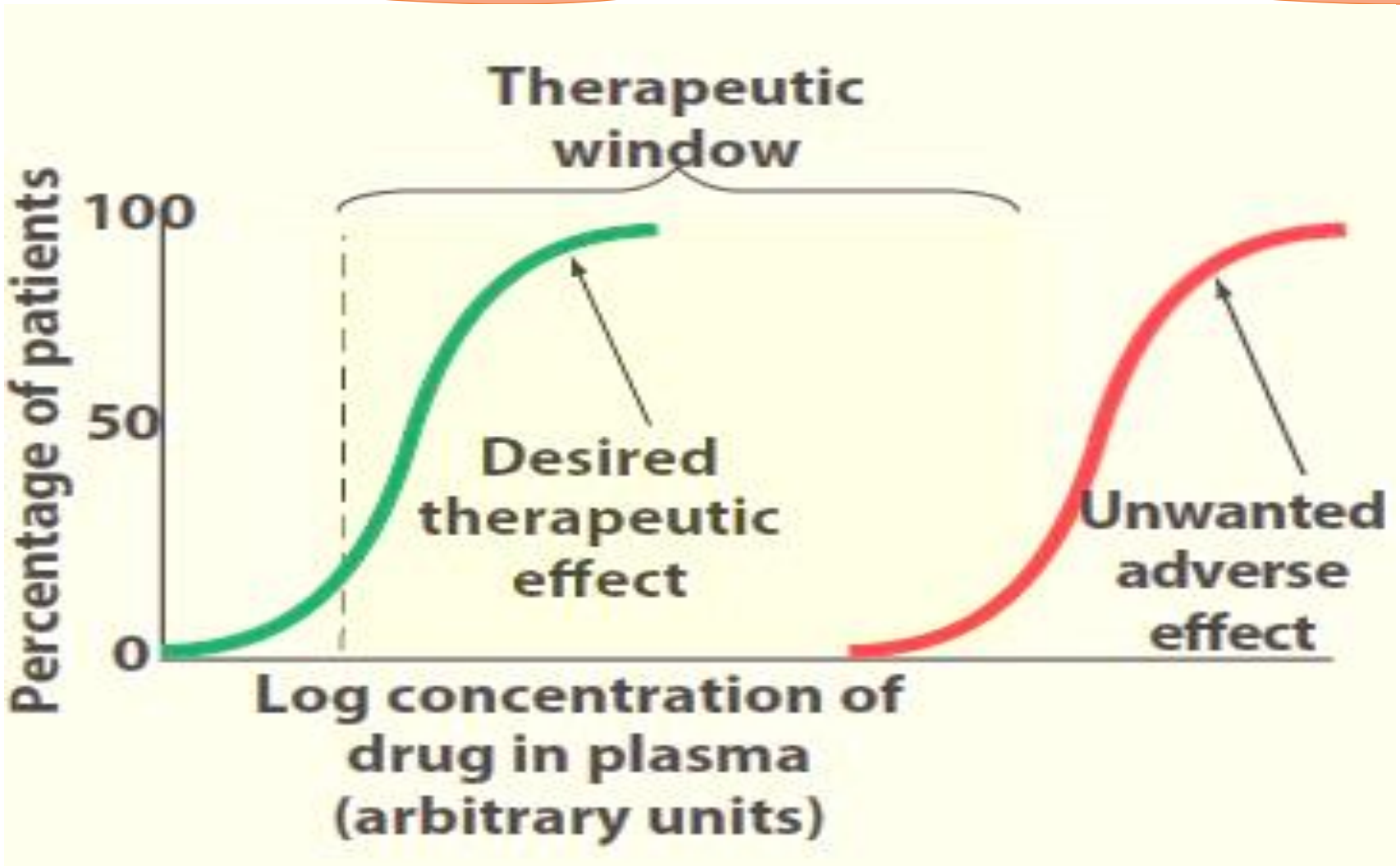
Ex histamine & epinephrine's

C. Chemical Antagonists

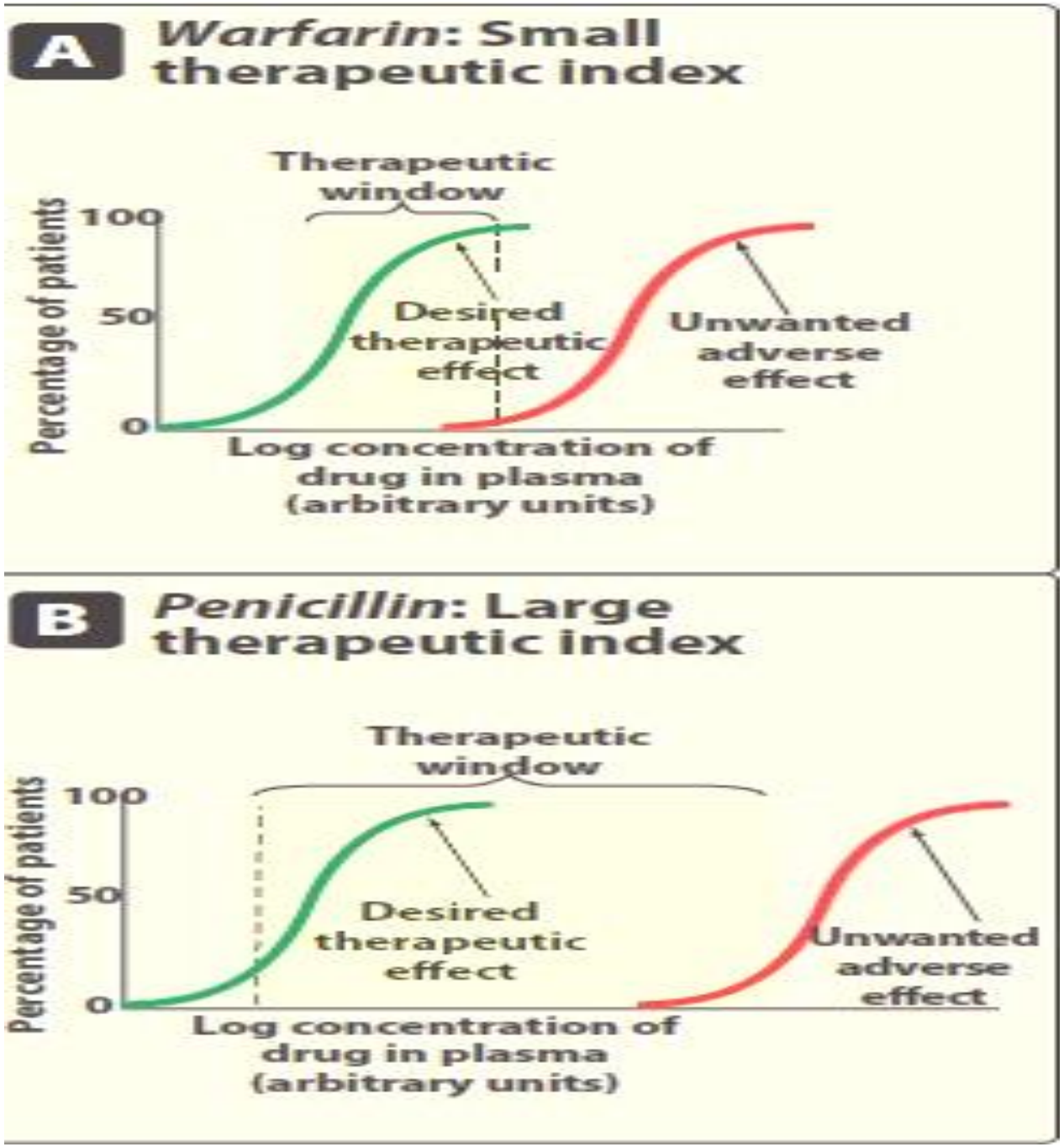
Ex Toxin & Charcoal

Pharmacodynamics

THERAPEUTIC INDEX & THERAPEUTIC WINDOW



Pharmacodynamics



Pharmacology

Pharmacokinetics

Pharmacokinetics

Pharmacokinetics

Pharmacokinetics denotes the effects of biologic systems on drugs. The major processes involved in pharmacokinetics are absorption, distribution, and elimination. Appropriate application of pharmacokinetic data and a few simple formulas makes it possible to calculate loading and maintenance doses.

Pharmacokinetics

THE MOVEMENT OF DRUGS IN THE BODY

- To reach its receptors and bring about a biologic effect, a drug molecule (eg, a benzodiazepine sedative) must travel from the site of administration (eg, the gastrointestinal tract) to the site of action (eg, the brain).
- **A-Permeation**
- Permeation is the movement of drug molecules into and within the biologic environment. It involves several processes.

Pharmacokinetics

1. Aqueous diffusion

Aqueous diffusion is the movement of molecules through the watery extracellular and intracellular spaces. The membranes of most capillaries have small water-filled pores that permit the aqueous diffusion of molecules up to the size of small proteins between the blood and the extravascular space.

2. Lipid diffusion

Lipid diffusion is the passive movement of molecules through membranes and other lipid structures. Like aqueous diffusion, this process is governed by Fick's law.

3. Transport by special carriers

Drugs that do not readily diffuse through membranes may be transported across barriers by mechanisms that carry similar endogenous substances. A very large number of such transporter molecules have been identified, and many of these are important in the movement of drugs or as targets of drug action.

4. Endocytosis & pinocytosis

Endocytosis occurs through binding of the transported molecule to specialized components (receptors) on cell membranes, with subsequent internalization by infoldings of that area of the membrane. The contents of the resulting intracellular vesicle are subsequently released into the cytoplasm of the cell. Endocytosis permits very large or very lipid-insoluble chemicals to enter cells. For example, large molecules such as proteins may cross cell membranes by endocytosis.

B. Fick's Law of Diffusion

Fick's law predicts the rate of movement of molecules across a barrier. The concentration gradient (C1 – C2) and permeability coefficient for the drug and the area and thickness of the barrier membrane are used to compute the rate as follows:

$$\text{Rate} = (C_1 - C_2) \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area}$$

B. Fick's Law of Diffusion

❖Thus, drug absorption is faster from organs with large surface areas, such as the small intestine, than from organs with smaller absorbing areas (the stomach). Furthermore, drug absorption is faster from organs with thin membrane barriers (eg, the lung) than from those with thick barriers (eg, the skin).

Pharmacokinetics

ABSORPTION OF DRUGS

Pharmacokinetics

A. Routes of Administration

- Drugs usually enter the body at sites remote from the target tissue or organ and thus require transport by the circulation to the intended site of action. To enter the bloodstream, a drug must be absorbed from its site of administration (unless the drug has been injected directly into the vascular compartment). The rate and efficiency of absorption differ depending on a drug's route of administration.
- The amount absorbed into the systemic circulation divided by the amount of drug administered constitutes its **bioavailability** by that route.

B. Blood Flow

- Blood flow influences absorption from intramuscular and subcutaneous sites and, in shock, from the gastrointestinal tract as well. High blood flow maintains a high drug depot–to–blood concentration gradient and thus facilitates absorption.

Pharmacokinetics

C. Concentration

- The concentration of drug at the site of administration is important in determining the concentration gradient relative to the blood. As indicated by Fick's law (Equation 1), the concentration gradient is a major determinant of the rate of absorption. Drug concentration in the vehicle is particularly important in the absorption of drugs applied topically.

Pharmacokinetics

DISTRIBUTION OF DRUGS

A. Determinants of Distribution

1. Size of the organ

The size of the organ determines the concentration gradient between blood and the organ. For example, skeletal muscle can take up a large amount of drug because the concentration in the muscle tissue remains low (and the blood tissue gradient high) even after relatively large amounts of drug have been transferred; this occurs because skeletal muscle is a very large organ.

2. Blood flow

Blood flow to the tissue is an important determinant of the rate of uptake of drug, although blood flow may not affect the amount of drug in the tissue at equilibrium. As a result, well-perfused tissues (eg, brain, heart, kidneys, and splanchnic organs) usually achieve high tissue concentrations sooner than poorly perfused tissues (eg, fat, bone).

3. Solubility

The solubility of a drug in tissue influences the concentration of the drug in the extracellular fluid surrounding the blood vessels. If the drug is very soluble in the cells, the concentration in the perivascular extracellular space will be lower and diffusion from the vessel into the extravascular tissue space will be facilitated. For example, some organs (such as the brain) have a high lipid content and thus dissolve a high concentration of lipid soluble agents rapidly.

Pharmacokinetics

4. Binding

Binding of a drug to macromolecules in the blood or a tissue compartment tends to increase the drug's concentration in that compartment. For example, warfarin is strongly bound to plasma albumin, which restricts warfarin's diffusion out of the vascular compartment. Conversely, chloroquine is strongly bound to extravascular tissue proteins, which results in a marked reduction in the plasma concentration of chloroquine.

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B. Apparent Volume of Distribution and Physical Volumes

Pharmacokinetics

- The apparent volume of distribution (Vd) is an important pharmacokinetic parameter that reflects the above determinants of the distribution of a drug in the body. Vd relates the amount of drug in the body to the concentration in the plasma.

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$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}}$$

(Units = Volume)

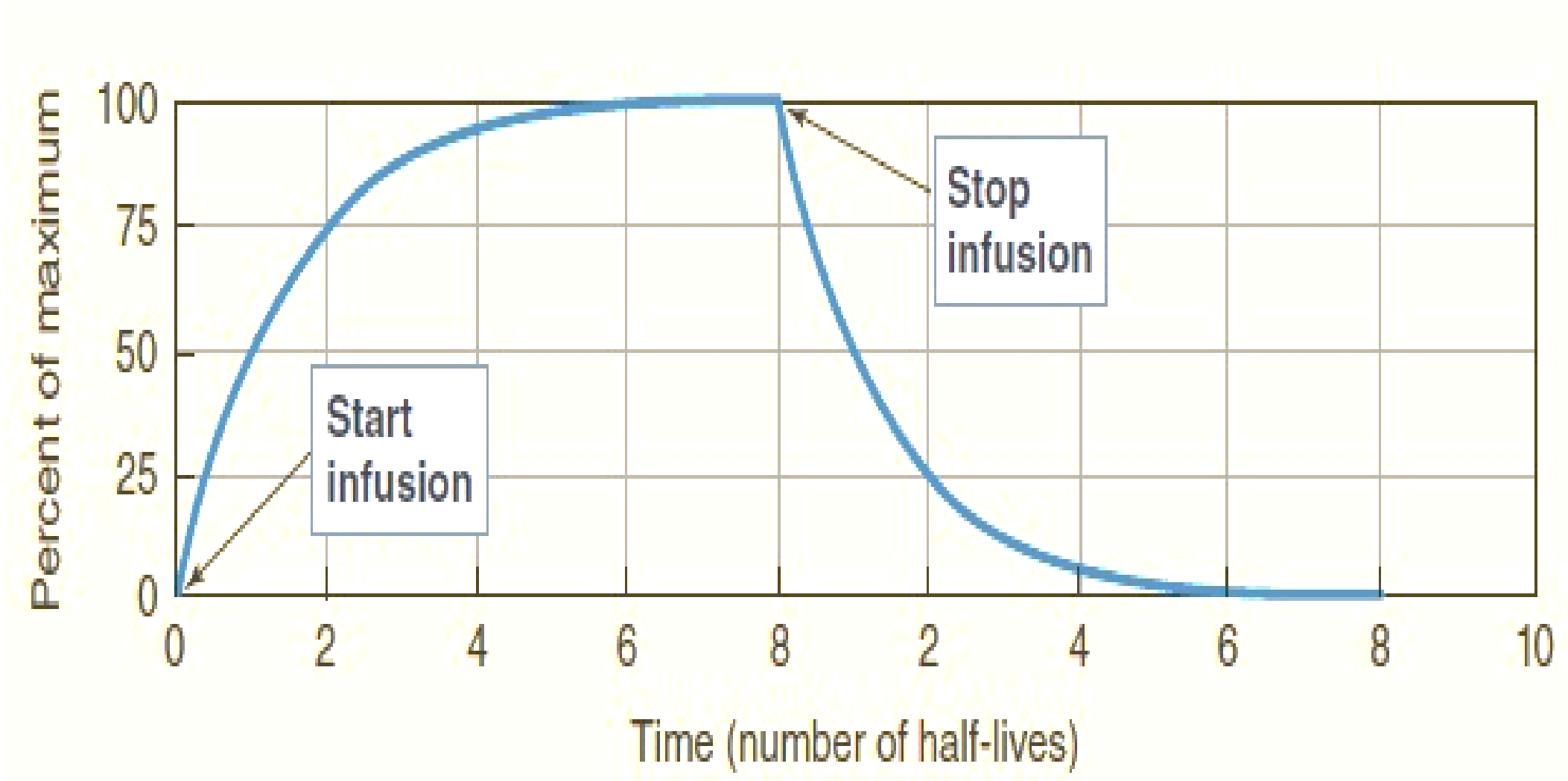
Pharmacokinetics

HALF-LIFE

Pharmacokinetics

- Half-life ($t1/2$) is a derived parameter, completely determined by Vd and CL. Like clearance, half-life is a constant for drugs that follow first-order kinetics. Half-life can be determined graphically from a plot of the blood level versus time.
- The half-life determines the rate at which blood concentration rises during a constant infusion and falls after administration is stopped.
- The effect of a drug at 87–90% of its steady-state concentration is clinically indistinguishable from the steady-state effect; thus, 3–4 half-lives of dosing at a constant rate are considered adequate to produce the effect.

Pharmacokinetics



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BIOAVAILABILITY

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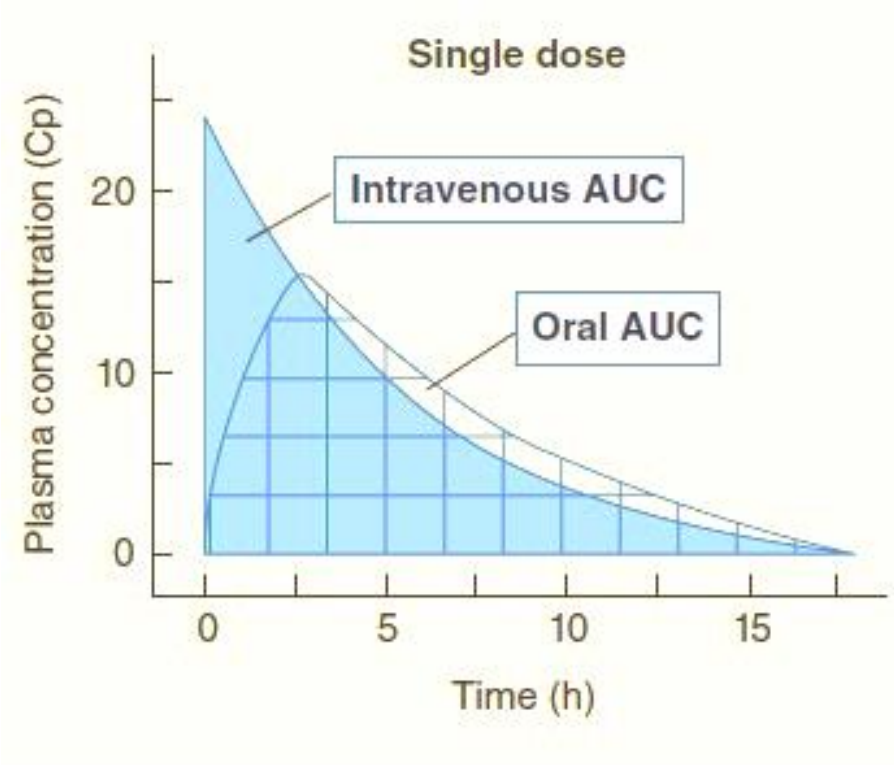
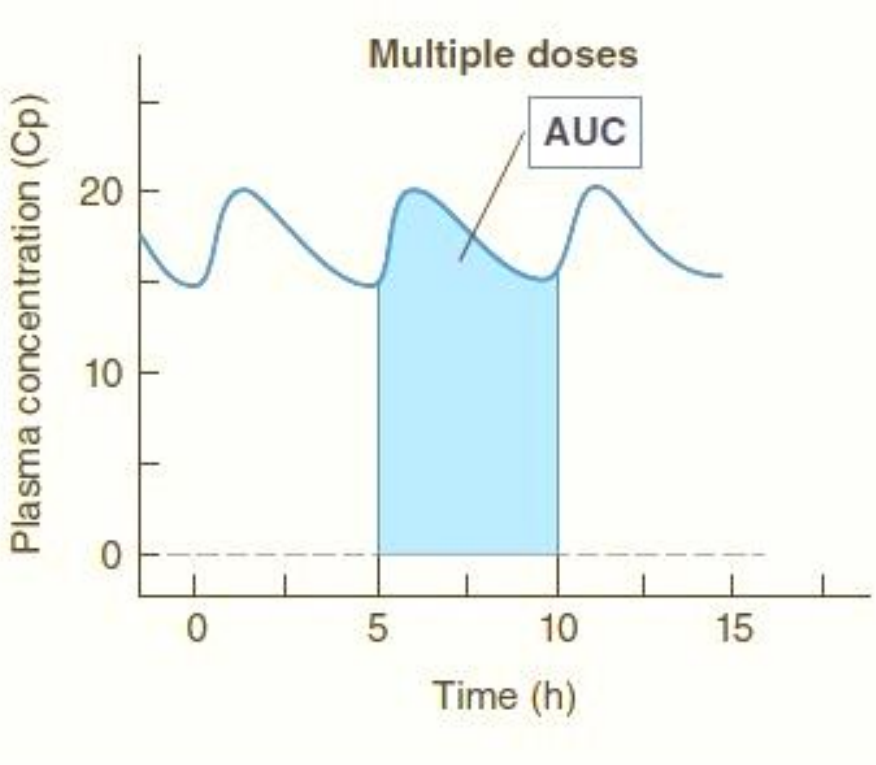
- The bioavailability of a drug is the fraction (F) of the administered dose that reaches the systemic circulation. Bioavailability is defined as unity (or 100%) in the case of intravenous administration. After administration by other routes, bioavailability is generally reduced by incomplete absorption (and in the intestine, expulsion of drug by intestinal transporters), first-pass metabolism, and any distribution into other tissues that occurs before the drug enters the systemic circulation.
- To account for such factors, the concentration appearing in the plasma is integrated over time to obtain an integrated total **area under the plasma concentration curve**.

Pharmacokinetics





Pharmacokinetics

METABOLISM OF DRUGS

Pharmacokinetics

- Drug **disposition** is sometimes used to refer to metabolism and elimination of drugs.
- Metabolism of a drug sometimes terminates its action, but other effects of drug metabolism are also important. Some drugs when given orally are metabolized before they enter the systemic circulation.
- Drug metabolism occurs primarily in the liver and less in kidney.

Pharmacokinetics

A. Drug Metabolism as a Mechanism of Termination of Drug Action

The action of many drugs (eg, sympathomimetics, phenothiazines) is terminated before they are excreted because they are metabolized to biologically inactive derivatives. Conversion to a metabolite is a form of **elimination**.

B. Drug Metabolism as a Mechanism of Drug Activation

Prodrugs (eg, levodopa, minoxidil) are inactive as administered and must be metabolized in the body to become active. Many drugs are active as administered and have active metabolites as well (eg, morphine, some benzodiazepines).

Pharmacokinetics

C. Drug Elimination Without Metabolism

Some drugs (eg, lithium, many others) are not modified by the body; they continue to act until they are excreted.

Pharmacokinetics

ELIMINATION OF DRUGS

Pharmacokinetics

- the rate of elimination following the last dose (disappearance of the active molecules from the site of action, the bloodstream, and the body) determines the duration of action for most drugs.
- Drug *elimination* is not the same as drug *excretion:* A drug may be eliminated by metabolism long before the modified molecules are excreted from the body.
- For most drugs and their metabolites, excretion is primarily by way of the kidney. Anesthetic gases, a major exception, are excreted primarily by the lungs.

Pharmacokinetics

- For drugs with active metabolites (eg, diazepam), elimination of the parent molecule by metabolism is not synonymous with termination of action. For drugs that are not metabolized, excretion is the mode of elimination.
- A small number of drugs combine irreversibly with their receptors, so that disappearance from the bloodstream is not equivalent to cessation of drug action. These drugs may have a very prolonged action.
- For example, phenoxybenzamine, an irreversible inhibitor of α adrenoceptors, is eliminated from the bloodstream in less than 1 h after administration. The drug's action, however, lasts for 48 h, the time required for turnover of the receptors.

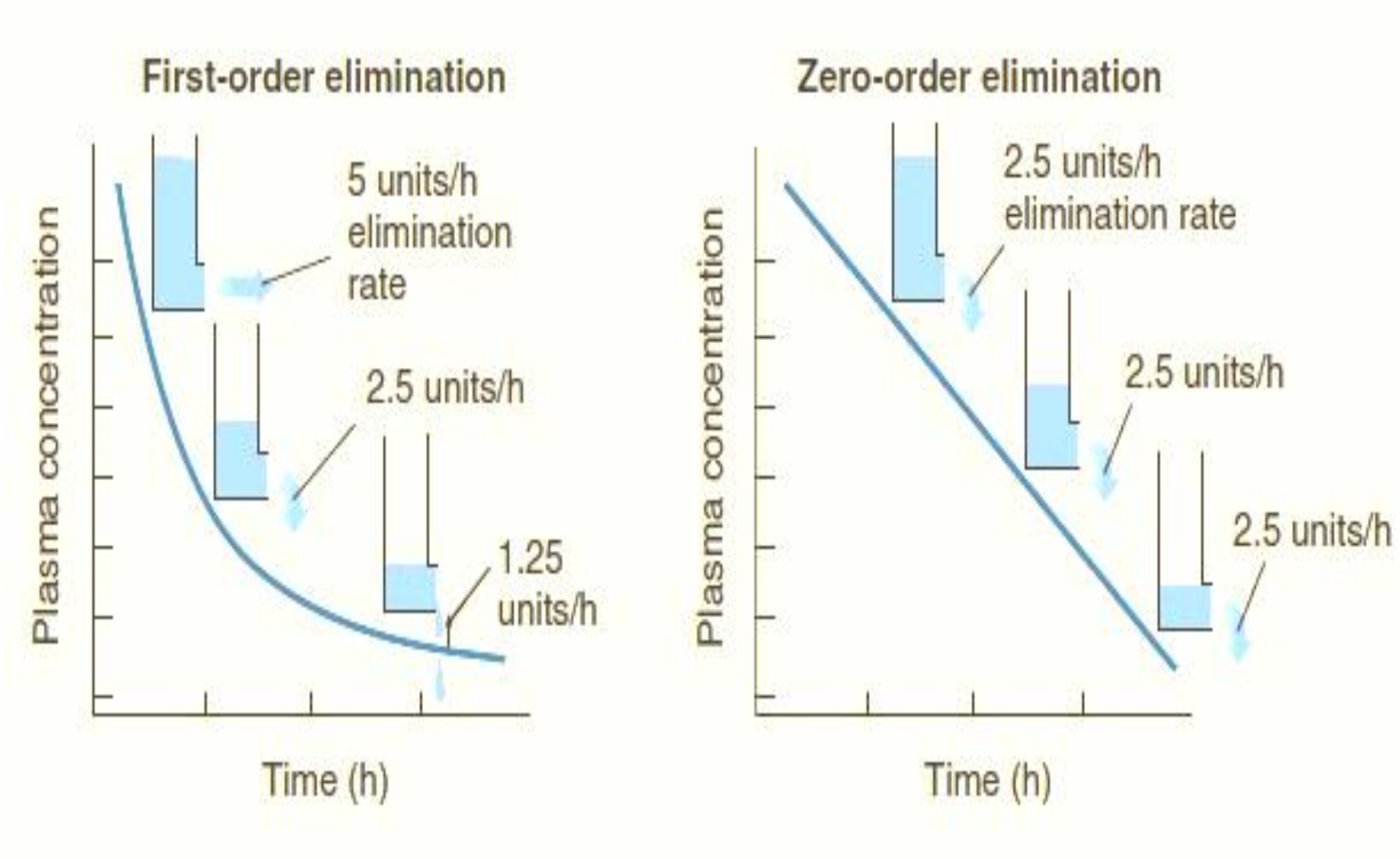
A. First-Order Elimination

- The term first-order elimination implies that the rate of elimination is proportional to the concentration (ie, the higher the concentration, the greater the amount of drug eliminated per unit time). The result is that the drug's concentration in plasma decreases exponentially with time.
- Drugs with first-order elimination have a characteristic half-life of elimination that is constant regardless of the amount of drug in the body. The concentration of such a drug in the blood will decrease by 50% for every half-life. Most drugs in clinical use demonstrate first-order kinetics.

B. Zero-Order Elimination

- The term zero-order elimination implies that the rate of elimination is constant regardless of concentration. This occurs with drugs that saturate their elimination mechanisms at concentrations of clinical interest.
- As a result, the concentrations of these drugs in plasma decrease in a linear fashion over time. This is typical of ethanol (over most of its plasma concentration range) and of phenytoin and aspirin at high therapeutic or toxic concentrations.

Pharmacokinetics

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