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Pharmacology（第6版）

Gary C. Rosenfeld
David S. Loose

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（第6版）

Gary C. Rosenfeld, PhD
Professor
Department of Integrated Biology and Pharmacology and
Graduate School of Biomedical Sciences
Assistant Dean for Education Programs
University of Texas Medical School at Houston
Houston, Texas

David S. Loose, PhD
Associate Professor
Department of Integrated Biology and Pharmacology and
Graduate School of Biomedical Sciences
University of Texas Medical School at Houston
Houston, Texas

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Preface

This concise review of medical pharmacology is designed for medical students, dental students, and others in the health care professions. It is intended primarily to help students prepare for licensing examinations, such as the United States Medical Licensing Examination Step 1 (USMLE) and other similar examinations. This book presents condensed and succinct descriptions of relevant and current Board-driven information pertaining to pharmacology without the usual associated details. It is not meant to be a substitute for the comprehensive presentation of information and difficult concepts found in standard pharmacology texts.

ORGANIZATION

The sixth edition begins with a chapter devoted to the general principles of drug action, followed by chapters concerned with drugs acting on the major body systems. Other chapters discuss autocoids, ergots, anti-inflammatory and immunosuppressive agents, drugs used to treat anemias and disorders of hemostasis, infectious diseases, cancer, and toxicology.

Each chapter includes a presentation of specific drugs with a discussion of their general properties, mechanism of action, pharmacologic effects, therapeutic uses, and adverse effects. A drug list, tables, and figures summarize essential drug information included in all chapters.

Clinically oriented, USMLE-style review questions and answers with explanations follow each chapter to help students assess their understanding of the information. Similarly, a comprehensive examination consisting of USMLE-style questions is included at the end of the book. This examination serves as a self-assessment tool to help students determine their fund of knowledge and diagnose any weaknesses in pharmacology.

Key Features

- Updated with current drug information
- End-of-chapter review tests feature updated USMLE-style questions
- Four-color tables and figures summarize essential information for quick recall
- Updated drug lists for each chapter
- Additional USMLE-style comprehensive examination questions and explanations

Gary C. Rosenfeld, PhD
David S. Loose, PhD

Contents

chapter 1

General Principles of Drug Action

I. DOSE–RESPONSE RELATIONSHIPS

A. Drug effects are produced by altering the normal functions of cells and tissues in the body via one of the four general mechanisms:

1. ***Interaction with receptors,*** naturally occurring target macromolecules that mediate the effects of endogenous physiologic substances such as neurotransmitters and hormones.

a. Figure 1.1 illustrates the four major classes of drug–receptor interactions, using specific examples of endogenous ligands.

(1) Ligand-activated ion channels. Figure 1.1A illustrates acetylcholine interacting with a nicotinic receptor that is a nonspecific Na^+/K^+ transmembrane ion channel. Interaction of a molecule of acetylcholine with each subunit of the channel produces a conformational change that permits the passage of Na^+ and K^+. Other channels that are targets for various drugs include specific Ca^{2+} and K^+ channels.

(2) G-protein–coupled receptors (Fig. 1.1B–D). G-protein–coupled receptors compose the largest class of receptors. All the receptors have seven transmembrane segments, three intracellular loops, and an intracellular carboxy-terminal tail. The biologic activity of the receptors is mediated via interaction with a number of G (GTP binding) proteins.

(a) $G\alpha_s$-coupled receptors. Figure 1.1B illustrates a β-adrenoceptor, which when activated by ligand binding (e.g., epinephrine) exchanges GDP for GTP. This facilitates the migration of $G\alpha_s$ ($G\alpha_{stimulatory}$) and its interaction with adenylyl cyclase (AC). $G\alpha_s$-bound AC catalyzes the production of cyclic AMP (cAMP) from adenosine triphosphate (ATP); cAMP activates protein kinase A, which subsequently acts to phosphorylate and activate a number of effector proteins. The βγ dimer may also activate some effectors. Hydrolysis of the guanosine triphosphate (GTP) bound to the Gα to guanosine diphosphate (GDP) terminates the signal.

(b) $G\alpha_i$ ($G_{inhibitory}$)-coupled receptors (Fig. 1.1C). Ligand binding (e.g., somatostatin) to $G\alpha_i$ ($G\alpha_{inhibitory}$)-coupled receptors similarly exchanges GTP for GDP, but $G\alpha_i$ inhibits AC, leading to reduced cAMP production.

(c) G_q (and G_{11})-coupled receptors (Fig. 1.1D). G_q (and G_{11}) interact with ligand (e.g., serotonin)-activated receptors and increase the activity of phospholipase C (PLC). PLC cleaves the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3). DAG activates protein kinase C, which can subsequently phosphorylate and activate a number of cellular proteins; IP_3 causes the release of Ca^{2+} from the endoplasmic reticulum into the cytoplasm, where it can activate many cellular processes.

(3) Receptor-activated tyrosine kinases (Fig. 1.1E). Many growth-related signals (e.g., insulin) are mediated via membrane receptors that possess intrinsic tyrosine kinase activity as illustrated for the insulin receptor. Ligand binding

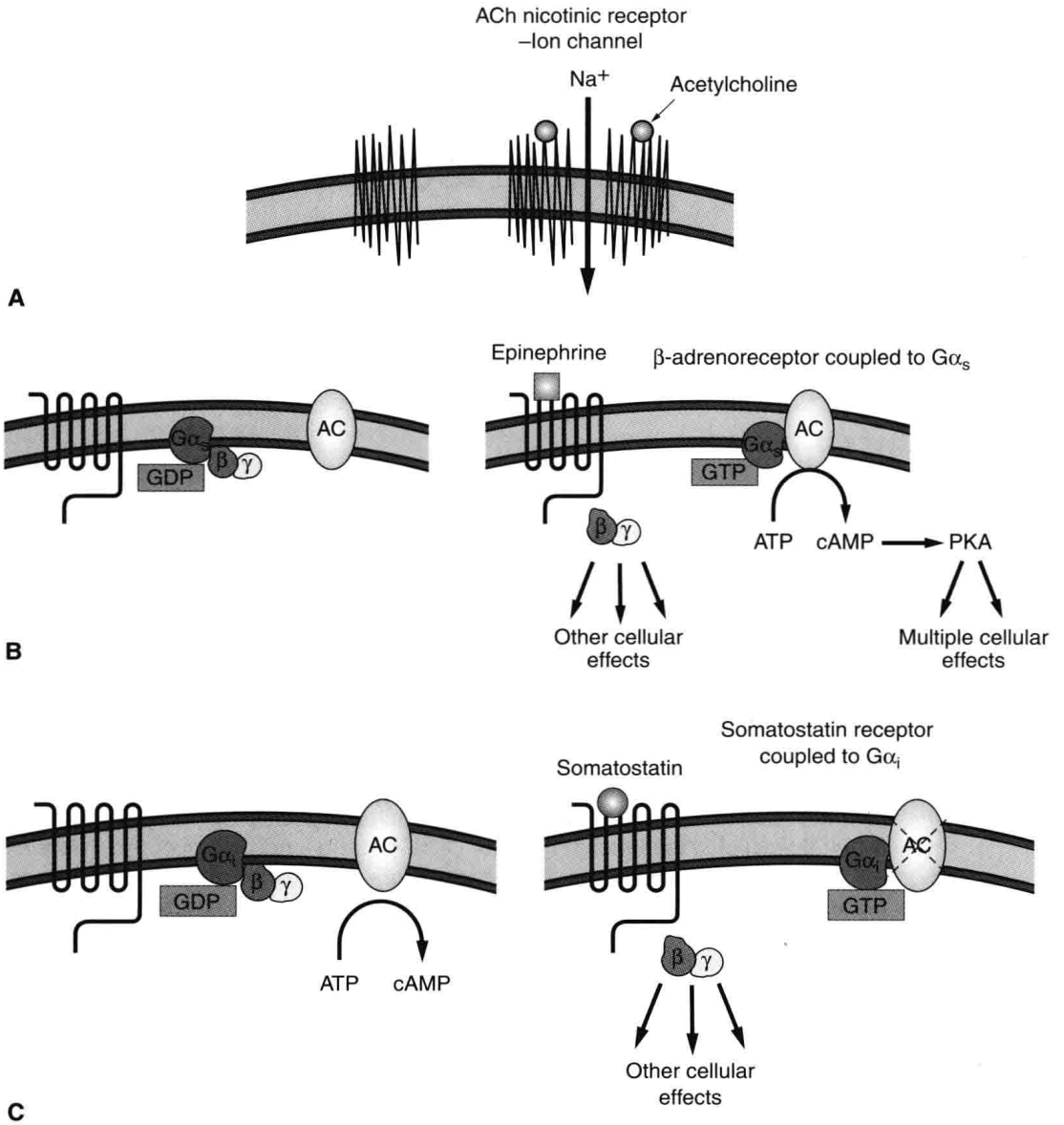

FIGURE 1.1. Four major classes of drug–receptor interactions, with specific examples of endogenous ligands. **A.** Acetylcholine interaction with a nicotinic receptor, a ligand-activated ion channel. **B–D.** G-protein–coupled receptors. **B.** Epinephrine interaction with a $G\alpha_s$-coupled β-adrenoceptor. **C.** Somatostatin interaction with a $G\alpha_i$ ($G_{inhibitory}$)-coupled receptor. **D.** Serotonin interaction with a G_q (and G_{11})-coupled receptor. **E.** Insulin interaction with a receptor-activated tyrosine kinase. **F.** Cortisol interaction with an intracellular nuclear receptor.

causes conformational changes in the receptor; some receptor tyrosine kinases are monomers that dimerize upon ligand binding. The liganded receptors then autophosphorylate tyrosine residues, which recruit cytoplasmic proteins to the plasma membrane where they are also tyrosine phosphorylated and activated.

(4) Intracellular nuclear receptors (Fig. 1.1F). Ligands (e.g., cortisol) for nuclear receptors are lipophilic and can diffuse rapidly through the plasma membrane. In the absence of ligand, nuclear receptors are inactive because of their interaction with chaperone proteins such as heat-shock proteins like HSP-90. Binding of ligand promotes structural changes in the receptor that facilitate dissociation of

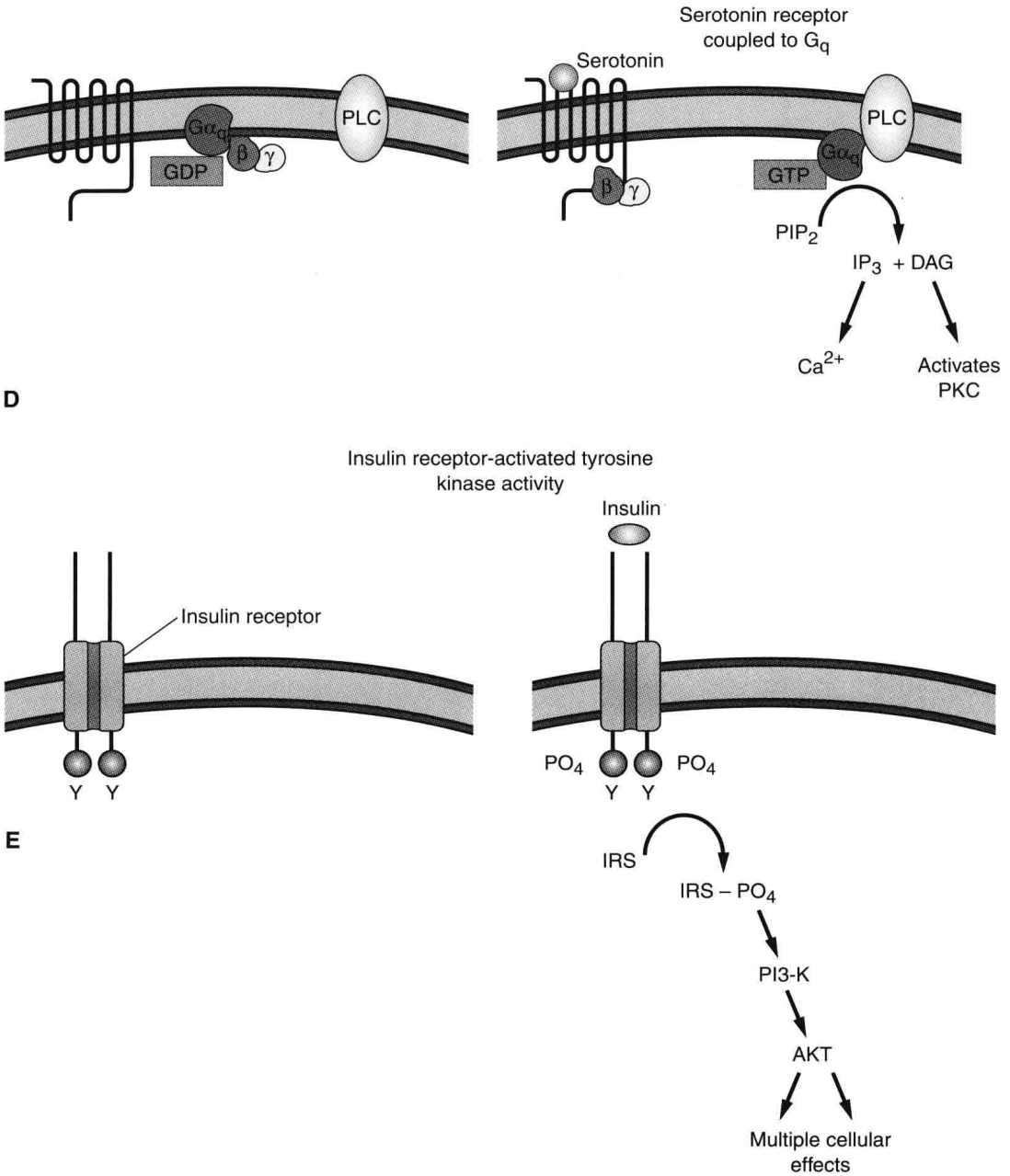

FIGURE 1.1. (*continued*).

chaperones, entry of receptors into the nucleus, hetero- or homodimerization of receptors, and high-affinity interaction with the DNA of target genes. DNA-bound nuclear receptors are able to recruit a diverse number of proteins called coactivators, which subsequently act to increase transcription of the target gene.

2. ***Alteration of the activity of enzymes*** by activation or inhibition of the enzyme's catalytic activity.
3. ***Antimetabolite action*** in which the drug, acting as a nonfunctional analog of a naturally occurring metabolite, interferes with normal metabolism.
4. ***Nonspecific chemical or physical interactions*** such as those caused by antacids, osmotic agents, and chelators.

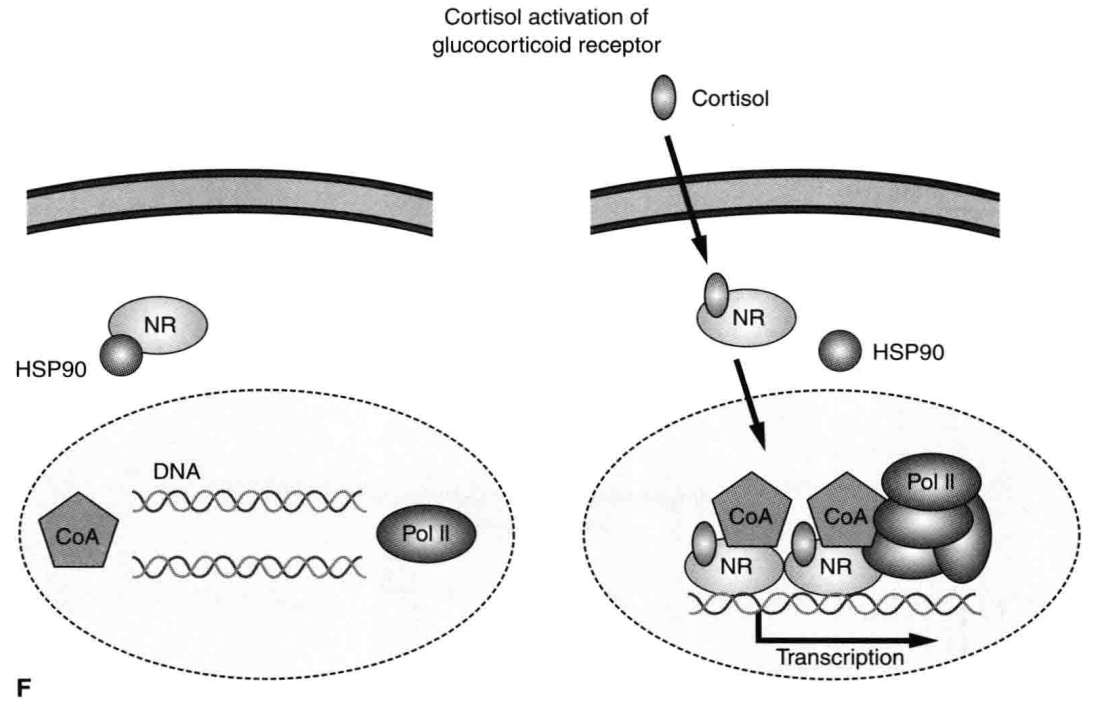

FIGURE 1.1. (*continued*).

B. **The graded dose–response curve** expresses an individual's response to increasing doses of a given drug. The magnitude of a pharmacologic response is proportional to the number of receptors with which a drug effectively interacts (Fig. 1.2). The graded dose–response curve includes the following parameters:

1. ***Magnitude of response*** is graded; that is, it continuously increases with the dose up to the maximal capacity of the system, and it is often depicted as a function of the logarithm of the dose administered (to see the relationship over a wide range of doses).
2. ***ED_{50}*** is the dose that produces the half-maximal response; the threshold dose is that which produces the first noticeable effect.
3. ***Intrinsic activity*** is the ability of a drug once bound to activate the receptor.
   a. **Agonists** are drugs capable of binding to, and activating, a receptor.
      (1) **Full agonists** occupy receptors to cause maximal activation; intrinsic activity = 1.

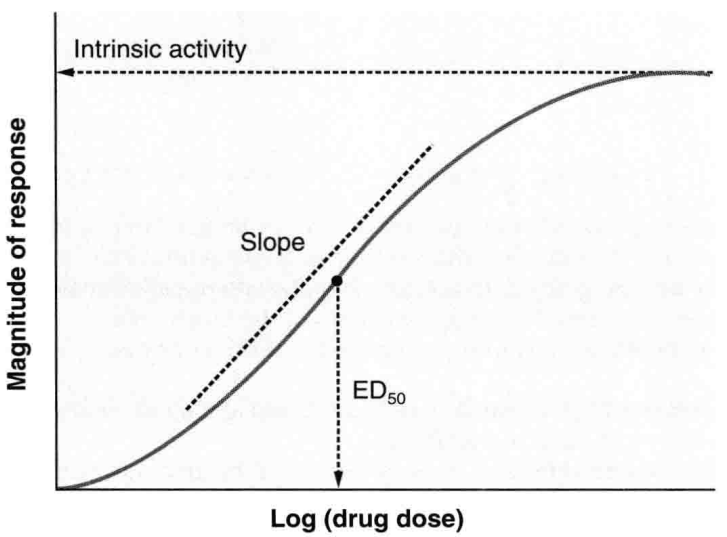

FIGURE 1.2. Graded dose–response curve.

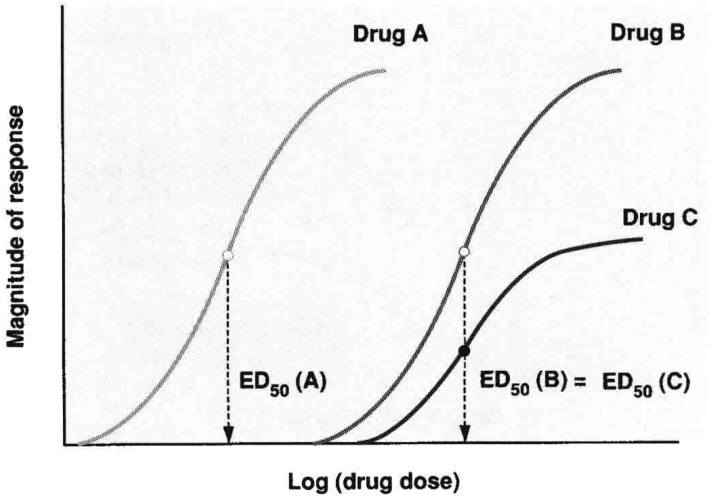

FIGURE 1.3. Graded dose–response curves for two agonists (**A** and **B**) and a partial agonist (**C**).

(2) **Partial agonists** can occupy receptors but cannot elicit a maximal response. Such drugs have an intrinsic activity of <1 (Fig. 1.3; drug C).

b. Antagonists bind to the receptor but do not initiate a response; that is, they block the action of an agonist or endogenous substance that works through the receptor.

(1) **Competitive antagonists** combine with the same site on the receptor but their binding does not activate the receptor (i.e., their intrinsic activity = 0) so they have no efficacy *per se* but may cause a pharmacological response in some cases by inhibiting the actions of endogenous substances or other drugs. Competitive antagonists may be reversible or irreversible. Reversible, or equilibrium, competitive antagonists are not covalently bound, shift the dose–response curve for the agonist to the right, and increase the ED_{50}; that is, more agonist is required to elicit a response in the presence of the antagonist (Fig. 1.4). Because higher doses of agonist can overcome the inhibition, the maximal response can still be obtained.

(2) **Noncompetitive antagonists** bind to the receptor at a site other than the agonist-binding site (Fig. 1.5) and either prevent the agonist from binding correctly or prevent it from activating the receptor. Consequently, the effective amount of receptor is reduced. Receptors unoccupied by antagonist retain the same affinity for agonist, and the ED_{50} is unchanged.

4. *Potency of a drug* is the relative measure of the amount of a drug required to produce a specified level of response (e.g., 50%) compared with other drugs that produce the same effect via the same receptor mechanism. The potency of a drug is determined by the **affinity** of a drug for its receptor and the amount of administered drug that reaches the

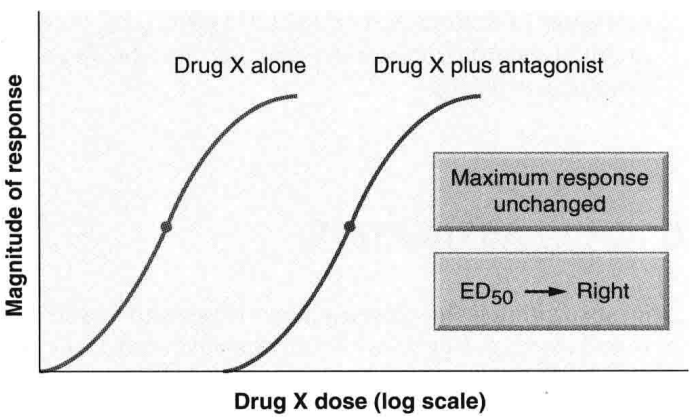

FIGURE 1.4. Graded dose–response curves illustrating the effects of competitive antagonists.

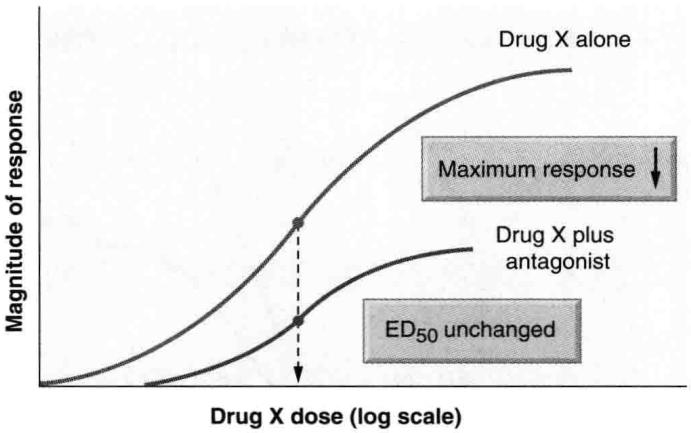

FIGURE 1.5. Graded dose–response curves illustrating the effects of noncompetitive antagonists.

receptor site. The relative potency of a drug can be demonstrated by comparing the ED_{50} values of two full agonists; the drug with the lower ED_{50} is more potent. (For example, in Fig. 1.3, drug A is more potent than drug B.)

5. ***The efficacy of a drug*** is the ability of a drug to elicit the pharmacologic response. Efficacy may be affected by such factors as the number of drug–receptor complexes formed, the ability of the drug to activate the receptor once it is bound (i.e., the drug's intrinsic activity), and the status of the target organ or cell.
6. ***Slope*** is measured at the mid-portion of the dose–response curve. The slope varies for different drugs and different responses. Steep dose–response curves indicate that a small change in dose produces a large change in response.
7. ***Variability*** reflects the differences between individuals in response to a given drug.
8. ***Therapeutic index (TI)*** relates the desired therapeutic effect to undesired toxicity; it is determined using data provided by the quantal dose–response curve. The TI is defined as TD_{50}/ED_{50} (i.e., the ratio of the dose that produces a toxic effect in half of the population to the dose that produces the desired effect in half of the population). Note that the TI should be used with caution in instances when the quantal dose–response curves for the desired and toxic effects are not parallel.

C. The quantal dose–response curve (Fig. 1.6A and B) relates the dosage of a drug to the frequency with which a designated response will occur within a population. The response may be an "all-or-none" phenomenon (e.g., individuals either do or do not fall asleep after receiving a sedative) or some predetermined intensity of effect. The quantal dose–response curve is obtained via transformation of the data used for a frequency distribution plot to reflect the cumulative frequency of a response. In the context of the quantal dose–response curve, ED_{50} indicates the dose of a drug that produces the response in half of the population. (Note that this differs from the meaning of ED_{50} in a graded dose–response curve.) For example, in Figure 1.6B, the ED_{50} would be 1. The TD_{50} for a drug would be determined from the midpoint of a similar curve indicating the cumulative percent of the population showing a toxic response to a drug.

II. DRUG ABSORPTION

Drug absorption is the movement of a drug from its site of administration into the bloodstream. In many cases, a drug must be transported across one or more biologic membranes to reach the bloodstream.