Principle of pharmacodynamics

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Learning Objectives:
At the end of sessions, students should be able to:

1. Define pharmacology and explain its importance for a clinician.
2. Define "drug receptor".
3. Explain the nature of drug receptors.
4. Describe other sites of drug actions.
5. Explain the drug-receptor interaction.
6. Define the terms "affinity", "intrinsic activity" and "Kd".
7. Explain the terms "agonist" and "antagonist" and their different types.
8. Explain chemical and physiological antagonists.
9. Explain the differences in drug responsiveness.
10. Explain tolerance, tachyphylaxis, and overshoot.
11. Define different dose-response curves.
12. Explain the information that can be obtained from a graded dose-response curve.
13. Describe the potency and efficacy of drugs.
14. Explain shift of dose-response curves in the presence of competitive and irreversible antagonists and its importance in clinical application of antagonists.
15. Explain the information that can be obtained from a quantal dose-response curve.
16. Define the terms ED50, TD50, LD50, therapeutic index and certain safety factor.

What is Pharmacology?It is defined as the study of drugs (substances used to prevent, diagnose, and treat disease). Pharmacology is the science that deals with the interactions betweena drug and the bodyor living systems.
The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed pharmacodynamicprocesses.These properties determine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called pharmacokinetic processes. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, a patient with impaired renal function.

Principle of Pharmacodynamics
Most drugs act by associating with specific macromolecules in ways that alter the macromolecules' biochemical or biophysical activities. This idea, more than a century old, is embodied in the term receptor: the component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug's observed effects.

Receptors and Inert Binding Sites
To function as a receptor, an endogenous molecule must first be selective in choosing ligands (drug molecules) to bind; and second, it must change its function upon binding in such a way that the function of the biologic system (cell, tissue, etc) is altered. The selectivity characteristic is required to avoid constant activation of the receptor by promiscuous binding of many different ligands. The ability to change function is clearly necessary if the ligand is to cause a pharmacologic effect. The body contains a vast array of molecules that are capable of binding drugs, however, and not all of these endogenous molecules are regulatory molecules. Binding of a drug to a non-regulatory molecule such as plasma albumin will result inno detectable change in the function of the biologic system, so this endogenous molecule can be called an inert binding site. Such binding is not completely without significance, however, because it affects the distribution of drug within the body and determines the amount of free drug in the circulation. Both of these factors are of pharmacokinetic importance.

Macromolecular Natureof Drug Receptors
Most receptors for clinically relevant drugs are proteins. The best-characterized drug receptors are regulatory proteins, which mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids, and hormones. This class of receptors mediates the effects of many of the most useful therapeutic agents.
Other classes of proteins that have been clearly identified as drug receptors include enzymes, which may be inhibited (or, less commonly, activated) by binding a drug (eg, cyclooxygenase,the receptor for aspirin); transport proteins (eg, Na+/K+-ATPase, the membrane receptor for cardioactive digitalis glycosides or chloride channel, the receptor for the sedative-hypnotic drug diazepam); and structural proteins (eg, tubulin, the receptor for colchicine, an anti-inflammatory agent).
Other macromolecular components of cells such as lipids and nucleotides can also act as receptors for drugs. For example, nystatin, an antifungal drug, binds ergostrol,the lipid of cell

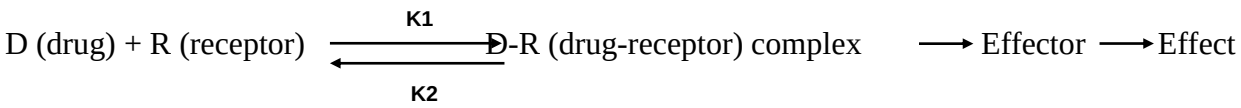
membranes of fungi; orcyclophosphamide, an anti-neoplastic agent, binds and alkylates DNAto disrupt cell division in the tumor.

Drug-Receptor Interaction

Drugs interact with receptors by means of chemical forces or bonds. These are of three major types: covalent, electrostatic, and hydrophobic. Covalent bonds are very strong and in many cases not reversible under biologic conditions. Thus, the covalent bond formed between the acetyl group of acetylsalicylic acid (aspirin) and cyclooxygenase, its enzyme target in platelets, is not readily broken. The platelet aggregation–blocking effect of aspirin lasts for long after free acetylsalicylic acid has disappeared from the bloodstream and is reversed only by the synthesis ofnew enzyme in new platelets, a process that takes several days.Therefore, drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized.

Electrostatic bonding is much more common than covalent bonding in drug-receptor interactions. Electrostatic bonds vary from relatively strong linkages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waals forces and similar phenomena.Electrostatic bonds are weaker than covalent bonds. Hydrophobic bonds are usually quite weak and are probablyimportant in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor "pockets."In cases of noncovalent binding, the effect lasts only as long as the drug occupies the receptor, and dissociation of drug from the receptor automatically terminates the effect. The duration of action of these drugs depend on their pharmacokinetic processes.

Most drugs must bind to a receptor to bring about an effect. However, at the cellular level, drug binding is only the first in a sequence of steps. When a drug binds a receptor, conformational changes occur in the receptor protein that represent the fundamental basis of receptor activation and the first of often many steps required to produce a pharmacologic response. The final change in function is accomplished by an effector mechanism. The effector may be part of the receptor molecule or may be a separate molecule. The overall transduction process that links drug occupancy of receptors and pharmacologic response is called coupling. A very large number of receptors communicate with their effectors through coupling molecules.



In process of drug-receptor interaction to produce an effect, two characteristic of drugs can be defined. 1. Affinity of a drug for a given receptor determines the tendency of a drug to bind a receptor. A drug may bind diverse receptors with different affinities, or various drugs may bind a particular receptor with different affinities. Affinity of a drug for a particular receptor has a reciprocal relation with its dissociation constant (Kd) which is the concentration of a drug at which 50% of receptors have been occupied. 2. Intrinsic activity of a drug defines as the ability of a drug to initiate a cellular effect following its binding to a receptor.

Types of Drug-Receptor Interactions

Drugs can be classified based on their action on the receptor:

Agonist:Agonist drugs have both affinity and intrinsic activity.When an agonist occupies a receptor,it regulates the function of receptor macromolecules; this means that it activates the receptor to signal as a direct result of binding to it. Some agonists activate a single kind of receptor to produce all their biologic functions, whereas others selectively promote one receptor function more than another.

Antagonist: Antagonist drugs have affinity but do not have intrinsic activity. That is, they bind to receptors but do not activate generation of a signal; consequently, they interfere with the ability of an agonist to bind and activate the receptor. Some of the most useful drugs in clinical medicine are pharmacologic antagonists.

Full Agonists, Partial Agonists, and Inverse Agonists

The receptor is postulated to exist in the inactive, nonfunctional form (Ri) and in the activated form (Ra). Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity. This effect, occurring in the absence of agonist, is termed constitutive activity. Agonists have a much higher affinity for the Ra configuration and stabilize it, so that a large percentage of the total pool resides in the Ra–D fraction and a large effect is produced. The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system. Many agonist drugs, when administered at concentrations sufficient to saturate the receptor pool, can activate their receptor effector systems to the maximum extent of which the system is capable; that is, they cause a shift of almost all of the receptor pool to the Ra–D pool. Such drugs are termed full agonists. Other drugs, called partial agonists, bind to the same receptors and activate them in the same way but do not evoke as great a response, no matter how high the concentration. Partial agonists do not stabilize the Ra configuration as fully as full agonists, so that a significant fraction of receptors exists in the Ri–D pool. Such drugs are said to have low intrinsic efficacy.Thus, pindolol, a β-adrenoceptor partial agonist, may act either as an agonist (if no full agonist is present) or as an antagonist (if a full agonist such as epinephrine is present). Intrinsic efficacy is independent of affinity (as usually measured) for the receptor. What will happen if a drug has a much stronger affinity for the Ri than for the Ra state and stabilizes a large fraction in the Ri–D pool? In this scenario the drug will reduce any constitutive activity, thus resulting in effects that are the opposite of the effects produced by conventional agonists at that receptor. Such drugs are termed inverse agonists. One of the best documented examples of such a system is the γ--aminobutyric acid (GABA-A) receptor-effector (a chloride channel) in the nervous system. This receptor is activated by the endogenous transmitter GABA and causes inhibition of postsynaptic cells. Conventional exogenous agonists such as benzodiazepines also facilitate the receptor-effector system and cause GABA-like inhibition with sedation as the therapeutic result. This sedation can be reversed by conventional neutral antagonists such as flumazenil. Inverse agonists of this receptor system cause anxiety and agitation, the inverse of sedation. Similar inverse agonists have been found for α-□adrenoceptors, histamine H1 and H2 receptors, and several other receptor systems.

Competitive & Irreversible Antagonists

Based on two-conformational model of receptors, conventional antagonists fix the fractions of drug-bound Ri and Ra in the same relative amounts as in the absence of any drug. In this situation, no change in activity will be observed, so the drug will appear to be without effect.

However, the presence of the antagonist at the receptor site will block access of agonists to the receptor and prevent the usual agonist effect. Such blocking action can be termed neutral antagonism.

Antagonist drugs are further divided into two classes depending on whether or not theyact *competitively* or *noncompetitively* relative to an agonist present at the same time.

In the presence of a fixed concentration of agonist, increasing concentrations of a competitive antagonist progressively inhibit the agonist response; high antagonist concentrations prevent response completely. Conversely, sufficiently high concentrations of agonist can surmount the effect of a given concentration of the antagonist.For example, atropine is a competitive antagonist of acetylcholine at muscarinic receptors that is, atropine prevents access of acetylcholine and similar agonist drugs to the muscarinic receptor site and stabilizes the receptor in its inactive state. Atropine reduces the effects of acetylcholineand similar molecules in the body, but its action can be overcome by increasing the dosage of agonist.

Some antagonists bind very tightly to the receptor site in an irreversible or pseudo-irreversible fashion and cannot be displaced by increasing the agonist concentration.

Drugs that bind to the same receptor molecule but do not prevent binding of the agonist are said to act allosterically and may enhance or inhibit (non-competitive antagonist) the action of the agonist molecule. Allosteric inhibition is not overcome by increasing the dose of agonist.

Other Mechanisms of Drug Antagonism

Not all mechanisms of antagonism involve interactions of drugs orendogenous ligands at a single type of receptor and some types ofantagonism do not involve a receptor at all. For example, protamine,a protein that is positively charged at physiologic pH, canbe used clinically to counteract the effects of heparin, an anticoagulantthat is negatively charged. In this case, one drug acts as achemical antagonist of the other simply by ionic binding thatmakes the other drug unavailable for interactions with proteinsinvolved in blood clotting.

Another type of antagonism is physiologic antagonism between endogenous regulatory pathways mediated by different receptors.For example, several catabolic actions of the glucocorticoid hormoneslead to increased blood sugar, an effect that is physiologicallyopposed by insulin. Although glucocorticoids and insulin act onquite distinct receptor-effector systems, the clinician must sometimesadminister insulin to oppose the hyperglycemic effects of aglucocorticoid hormone, whether the latter is elevated by endogenoussynthesis (eg, a tumor of the adrenal cortex) or as a result ofglucocorticoid therapy.

In general, use of a drug as a physiologic antagonist produceseffects that are less specific and less easy to control than are theeffects of a receptor-specific antagonist. Thus, for example, to treatbradycardia caused by increased release of acetylcholine fromvagus nerve endings, the physician could use isoproterenol, aβ-adrenoceptor agonist that increases heart rate by mimickingsympathetic stimulation of the heart. However, use of this physiologicantagonist would be less rational—and potentially moredangerous—than use of a receptor-specific antagonist such asatropine (a competitive antagonist at the receptors at which acetylcholineslows heart rate).

Alterations in Number or Function of Receptors

Experimental studies have documented changes in drug response caused by increases or decreases in the number of receptor sites orby alterations in the efficiency of coupling of receptors to distal effector mechanisms. In some cases, the change in receptor number is caused

by other hormones; for example, thyroid hormones increase both the number of β□receptors in rat heart muscle and cardiac sensitivity to catechol amines. Similar changes probably contribute to the tachycardia of thyrotoxicosis in patients and may account for the usefulness of propranolol, a β-adrenoceptor antagonist, in ameliorating symptoms of this disease.
In other cases, the agonist ligand itself induces a decrease in the number (eg, down-regulation) or coupling efficiency (eg, desensitization) of its receptors. These mechanisms may contribute to two clinically important phenomena: first, tachyphylaxis or tolerance to the effects of some drugs (eg, biogenic amines and their congeners), and second, the "overshoot" phenomena that follow withdrawal of certain drugs. These phenomena can occur with either agonists or antagonists.
With some drugs, the intensity of response to a given dose may change during the course of therapy; in these cases, responsiveness usually decreases as a consequence of continued drug administration, producing a state of relative tolerance to the drug's effects. When responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to tachyphylaxis.
An antagonist may increase the number of receptors in a critical cell or tissue by preventing down-regulation caused by an endogenous agonist. When the antagonist is withdrawn, the elevated number of receptors can produce an exaggerated response to physiologic concentrations of agonist. Potentially disastrous withdrawal symptoms can result for the opposite reason when administration of an agonist drug is discontinued. In this situation, the number of receptors, which has been decreased by drug-induced down-regulation, is too low for endogenous agonist to produce effective stimulation. For example, the withdrawal of clonidine (a drug whose α2-adrenoceptor agonist activity reduces blood pressure) can produce hypertensive crisis, probably because the drug down-regulates α2 adrenoceptors.

Variation in Drug Responsiveness

Individuals may vary considerably in their response to a drug; indeed, a single individual may respond differently to the same drug at different times during the course of treatment.
Occasionally, individuals exhibit an unusual or idiosyncratic drug response, one that is infrequently observed in most patients. The idiosyncratic responses are usually caused by genetic differences in metabolism of the drug or by immunologic mechanisms, including allergic reactions.
Quantitative variations in drug response are in general more common and more clinically important. An individual patient is hyporeactiveor hyperreactiveto a drug in that the intensity of effect of a given dose of drug is diminished or increased compared with the effect seen in most individuals. (Note: The term hypersensitivity usually refers to allergic or other immunologic responses to drugs.)

Concentration-Effect Curves & Receptor Binding of Agonists

Even in intact animals or patients, responses to low doses of a drug usually increase in direct proportion to dose. As doses increase, however, the response increment diminishes; finally, doses may be reached at which no further increase in response can be achieved. This relation between drug concentration and effect is traditionally described by a hyperbolic curve(Figure A) according to the following equation:

$$E = \frac{Emax \cdot C}{C + EC50}$$

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

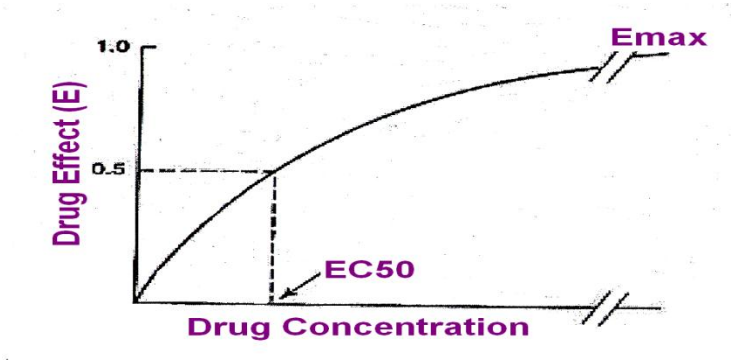


Figure A

This hyperbolic relation suggests that drug agonists act by binding to ("occupying") a distinct class of biologic molecules with a characteristic affinity for the drug receptor. In these systems, drug bound to receptors (B)relates to the concentration of free (unbound) drug (C) as depictedin Figure B and as described by an analogous equation:

$$B = \frac{Bmax \cdot C}{C + Kd}$$

in which Bmax indicates the total concentration of receptor sites(ie, sites bound to the drug at infinitely high concentrations offree drug) and Kd (the equilibrium dissociation constant) representsthe concentration of free drug at which half-maximal bindingis observed. This constant characterizes the receptor's affinityfor binding the drug in a reciprocal fashion: If the Kd is low,binding affinity is high, and vice versa.

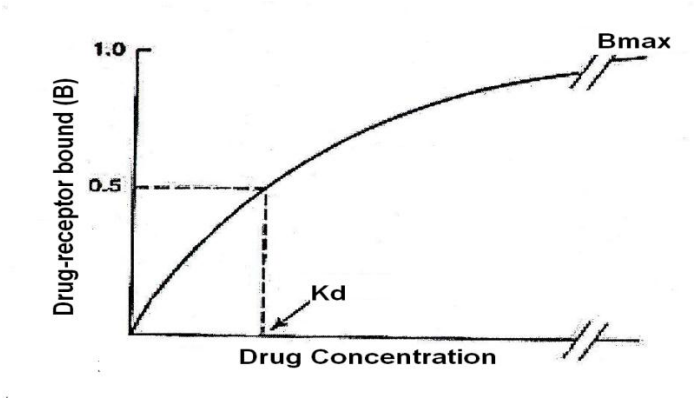


Figure B

Dose-response dataare often presented as a plot of the drug effect (ordinate) againstthe *logarithm* of the dose or concentration (abscissa), transformingthe hyperbolic curve of Figure A into a sigmoid curve with a linear midpoint. This transformation is convenientbecause it expands the scale of the concentration axis at low concentrations(where the effect is changing rapidly) and compresses it athigh concentrations (where the effect is changing slowly), but otherwisehas no biologic or pharmacologic significance portion (eg, Figure C).

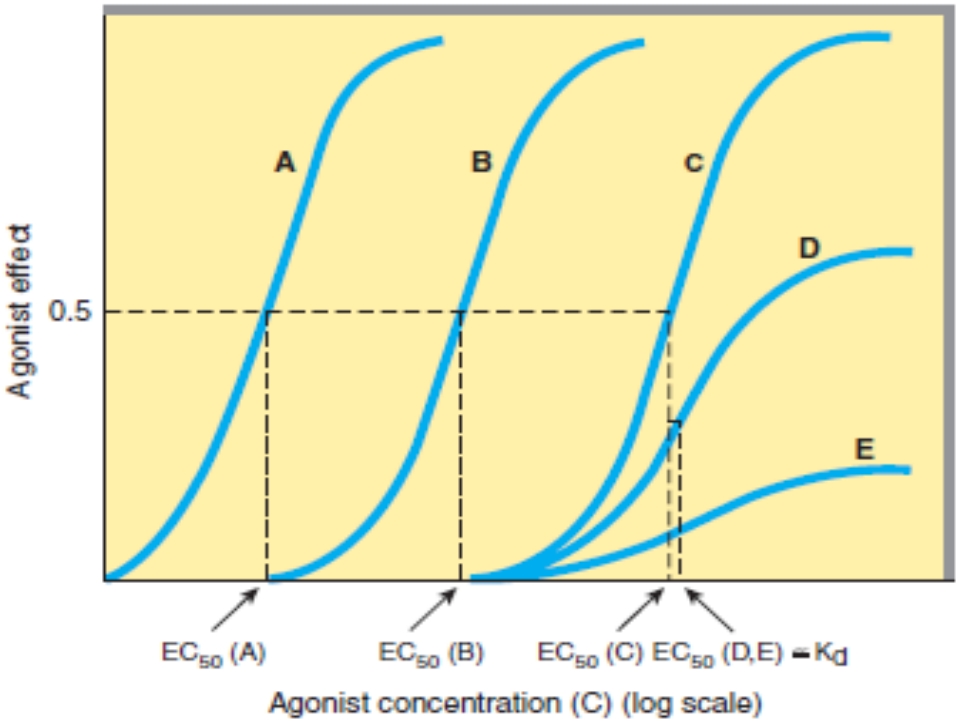


Figure C

RELATION BETWEEN DRUG DOSE& CLINICAL RESPONSE

To make rational therapeutic decisions, the prescriber must understandhow drug-receptor interactions underlie the relationsbetween dose and response in patients, the nature and causes ofvariation in pharmacologic responsiveness, and the clinical implicationsof selectivity of drug action.

Dose & Response in Patients

A. Graded Dose-Response Relations

To choose among drugs and to determine appropriate doses of a drug,the prescriber must know the relative pharmacologic potency and maximal efficacy of the drugs in relation to the desired therapeutic effect. These two important terms, often confusing to students and clinicians, can be explained by referring to Figure D, which depicts graded dose-response curves that relate the dose of four different drugs to the magnitude of a particular therapeutic effect.

1. Potency—Potency refers to the concentration (EC50) or dose (ED50) of a drug required to produce 50% of that drug's maximal effect. Thus, the pharmacologic potency of drug A in Figure D is less than that of drug B,a partial agonist because the EC50 of A is greater than the EC50 ofB. Potency of a drug depends in part on the affinity (Kd) of receptors for binding the drug and in part on the efficiency with which drug-receptor interaction is coupled to response. Note that some doses of drug A can produce larger effects than any dose of drug B, despite the fact that we describe drug B as pharmacologically more potent. The reason for this is that drug A has a larger maximal efficacy (as described below).

For therapeutic purposes, the potency of a drug should be stated in dosage units, usually in terms of a particular therapeutic end point (eg, 50 mg for mild sedation, 1 mcg/kg/min for an increase in heart rate of 25 bpm). Relative potency, the ratio of equi-effective doses (0.2, 10, etc), may be used in comparing one drug with another.

*2. Maximal efficacy:*This parameter reflects the limit of the dose-response relation on the response axis. Drugs A, C, and Din Figure D have equal maximal efficacy, and all have greatermaximal efficacy than drug B. The maximal efficacy (sometimes referred to simply as efficacy) of a drug is obviously crucial for making clinical decisions when a large response is needed. It may be determined by the drug's mode of interactions with receptors (as with partial agonists)□ □or by characteristics of the receptor effector system involved.Thus, diuretics that act on one portion of the nephron may produce much greater excretion of fluid and electrolytes than diuretics that act elsewhere. In addition, the *practical* efficacy of a drug for achieving a therapeutic end point (eg, increased cardiac contractility) may be limited by the drug's propensity to cause a toxic effect (eg, fatal cardiac arrhythmia) even if the drug could otherwise produce a greater therapeutic effect.

B. Shape of Dose-Response Curves

Although the responses depicted in curves A, B, and C of Figure D approximate the shape of a simple. Michaelis-Menten relation (transformed to a logarithmic plot), some clinical responses do not. Extremely steep dose-response curves (eg, curve D) may have important clinical consequences if the upper portion of the curve represents an undesirable extent of response (eg, coma caused by a sedative-hypnotic). Steep dose-response curves in patients can result from cooperative interactions of several different actions of a drug (eg, effects on brain, heart, and peripheralvessels, all contributing to lowering of blood pressure).

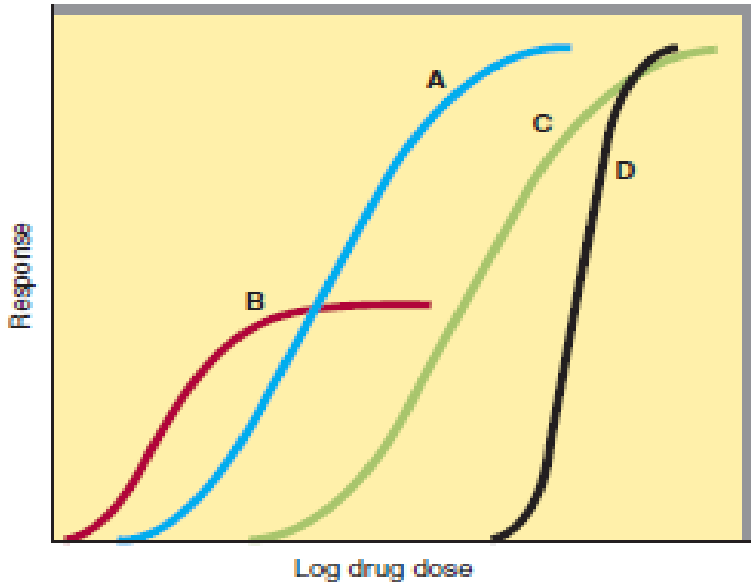


Figure D

In the presence of a fixed concentration of agonist, increasingconcentrations of a competitive antagonist progressively inhibitthe agonist response; high antagonist concentrations preventresponse completely. Conversely, sufficiently high concentrationsof agonist can surmount the effect of a given concentration of theantagonist; that is, the Emax for the agonist remains the same forany fixed concentration of antagonist (Figure E). Because theantagonism is competitive, the presence of antagonist increases theagonist concentration required for a given degree of response, andso the agonist concentration-effect curve is shifted to the right.

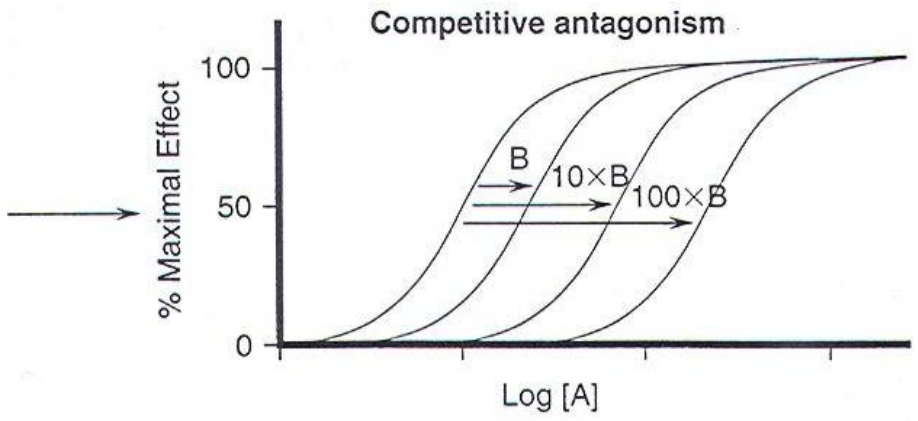


Figure E

For the clinician, this mathematical relation has two importanttherapeutic implications:
1. The degree of inhibition produced by a competitive antagonistdepends on the concentration of antagonist. The competitiveβ-adrenoceptor antagonist propranolol provides a usefulexample. Patients receiving a fixed dose of this drug exhibit awide range of plasma concentrations, owing to differencesamong individuals in clearance of propranolol. As a result,inhibitory effects on physiologic responses to norepinephrineand epinephrine (endogenous adrenergic receptor agonists)may vary widely, and the dose of propranolol must be adjustedaccordingly.
2. Clinical response to a competitive antagonist also depends onthe concentration of agonist that is competing for binding toreceptors. Again, propranolol provides a useful example: Whenthis drug is administered at moderate doses sufficient to blockthe effect of basal levels of the neurotransmitter norepinephrine,resting heart rate is decreased. However, the increase inthe release of norepinephrine and epinephrine that occurs withexercise, postural changes, or emotional stress may suffice toovercome this competitive antagonism. Accordingly, the samedose of propranolol may have little effect under these conditions,thereby altering therapeutic response.

The actions of a noncompetitive antagonist are different because, once a receptor is bound by such a drug,agonists cannotsurmount the inhibitory effect irrespective of their concentration.In many cases, noncompetitive antagonists bind to the receptorinan irreversible or nearly irreversible fashion, sometimes by forminga covalent bond with the receptor. After occupancy of someproportion of receptors by such an antagonist, the number ofremaining unoccupied receptors may be too low for the agonist(even at high concentrations) to elicit a response comparable tothe previous maximal response (Figure F).

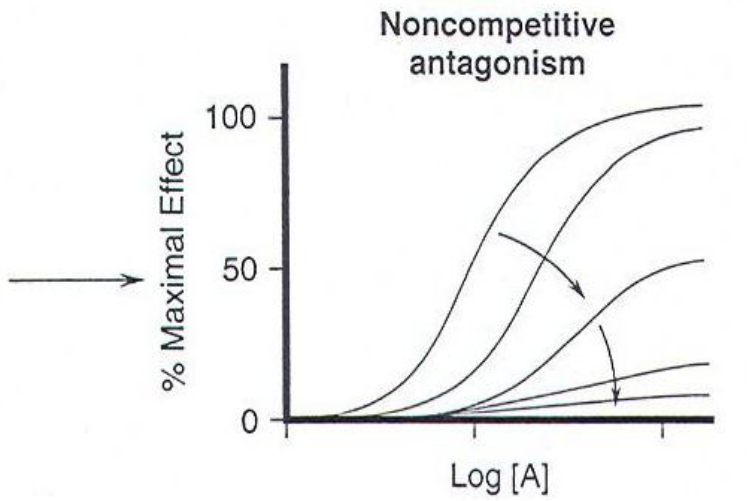


Figure F

Therapeutically, such irreversible antagonists present distinctadvantages and disadvantages. Once the irreversible antagonist has occupied the receptor, it need not be present in unbound form toinhibit agonist responses. Consequently, the duration of action ofsuch an irreversible antagonist is relatively independent of its ownrate of elimination and more dependent on the rate of turnover ofreceptor molecules.Phenoxybenzamine, an irreversible α-adrenoceptor antagonist,is used to control the hypertension caused by catecholaminesreleased from pheochromocytoma, a tumor of the adrenalmedulla. If administration of phenoxybenzamine lowers bloodpressure, blockade will be maintained even when the tumor episodicallyreleases very large amounts of catecholamine. In thiscase, the ability to prevent responses to varying and high concentrationsof agonist is a therapeutic advantage. If overdose occurs,however, a real problem may arise. If the α-adrenoceptor blockadecannot be overcome, excess effects of the drug must be antagonized"physiologically," ie, by using a pressor agent that does notact via α receptors

C. Quantal Dose-Effect Curves

Graded dose-response curves of the sort described above have certainlimitations in their application to clinical decision making. Forexample, such curves may be impossible to construct if the pharmacologicresponse is an either-or (quantal) event, such as preventionof convulsions, arrhythmia, or death. Furthermore, the clinicalrelevance of a quantitative dose-response relation in a singlepatient, no matter how precisely defined, may be limited in applicationto other patients, owing to the great potential variabilityamong patients in severity of disease and responsiveness to drugs.

Some of these difficulties may be avoided by determining thedose of drug required to produce a specified magnitude of effectin a large number of individual patients or experimental animalsand plotting the cumulative frequency distribution of respondersversus the log dose (Figure G). The specified quantal effect maybe chosen on the basis of clinical relevance (eg, relief of headache)or for preservation of safety of experimental subjects (eg, using lowdoses of a cardiac stimulant and specifying an increase in heart rateof 20 bpm as the quantal effect), or it may be an inherently quantalevent (eg, death of an experimental animal). For most drugs, thedoses required to produce a specified quantal effect in individualsare lognormally distributed; that is, a frequency distribution ofsuch responses plotted against the log of the dose produces agaussian normal curve of variation (FigureG).

When these responses are summated, the resulting cumulativefrequency distribution constitutes a quantal dose-effect curve (ordose-percent curve) of the proportion or percentage of individualswho exhibit the effect plotted as a function of log dose.

The quantal dose-effect curve is often characterized by statingthe median effective dose (ED50), which is the dose at which50% of individuals exhibit the specified quantal effect. (Note thatthe abbreviation ED50 has a different meaning in this context fromits meaning in relation to graded dose-effect curves, described inprevious text). Similarly, the dose required to produce a particulartoxic effect in 50% of animals is called the median toxic dose (TD50). If the toxic effect is death of the animal, a median lethaldose (LD50) may be experimentally defined. Such values providea convenient way of comparing the potencies of drugs in experimentaland clinical settings: Thus, if the ED50s of two drugs forproducing a specified quantal effect are 5 and 500 mg, respectively, then the first drug can be said to be 100 times more potentthan the second for that particular effect. Similarly, one can obtaina valuable index of the selectivity of a drug's action by comparingits ED50s for two different quantal effects in a population (eg,cough suppression versus sedation for opioid drugs).

Quantal dose-effect curves may also be used to generate informationregarding the margin of safety to be expected from a particulardrug used to produce a specified effect. One measure,which relates the dose of a drug required to produce a desiredeffect to that which produces an undesired effect, is the therapeuticindex. In animal studies, the therapeutic index is usuallydefined as the ratio of the TD50 to the ED50 for some therapeuticallyrelevant effect. The precision possible in animal experimentsmay make it useful to use such a therapeutic index to estimate thepotential benefit of a drug in humans. Of course, the therapeuticindex of a drug in humans is almost never known with real precision;instead, drug trials and accumulated clinical experience oftenreveal a range of usually effective doses and a different (but sometimesoverlapping) range of possibly toxic doses. The rangebetween the minimum toxic dose and the minimum therapeuticdose is called the therapeutic window and is of greater practicalvalue in choosing the dose for a patient. The clinically acceptablerisk of toxicity depends critically on the severity of the disease beingtreated. For example, the dose range that provides relief from anordinary headache in the majority of patients should be very muchlower than the dose range that produces serious toxicity, even if thetoxicity occurs in a small minority of patients. However, for treatmentof a lethal disease such as Hodgkin's lymphoma, the acceptabledifference between therapeutic and toxic doses may be smaller.Finally, note that the quantal dose-effect curve and the gradeddose-response curve summarize somewhat different sets of information,although both appear sigmoid in shape on a semilogarithmicplot (compare Figures F and G). Critical informationrequired for making rational therapeutic decisions can be obtainedfrom each type of curve. Both curves provide information regardingthe potency and selectivity of drugs; the graded dose-responsecurve indicates the maximal efficacy of a drug, and the quantaldose-effect curve indicates the potential variability of responsivenessamong individuals.