Pharmacodynamic Interactions: Core Concepts

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Abstract
This chapter discusses the essential terms and concepts pertaining to the relationship between the concentration of a drug at the end-organ site and the degree of drug effect. This subset of pharmacology is known as **pharmacodynamics**.

Introduction to Pharmacodynamics

Pharmacodynamics is commonly described as "what a drug does to the body" and this concept includes biochemical and physiological actions resulting from the administration of a drug. In contrast, *pharmacokinetics* describes "what the body does to a drug" (ie, absorption, distribution, metabolism, or excretion). Pharmacodynamics describes the relation between the concentration of drug at the effect site and the degree of the resulting drug effect. Dose-response relations may demonstrate the pharmacodynamic effects of a single drug or allow comparison of different drugs. Graphic illustrations often show the relations between dosage along the x-axis and the degree of the response to the drug (efficacy) along the y-axis. The effects may be intended (therapeutic), unintended (adverse effects), or supratherapeutic (toxicity). Clinically, the drug concentration is targeted for the therapeutic window through proper dosage, thereby maximizing therapeutic effects while minimizing adverse effects (Fig. 2.1).

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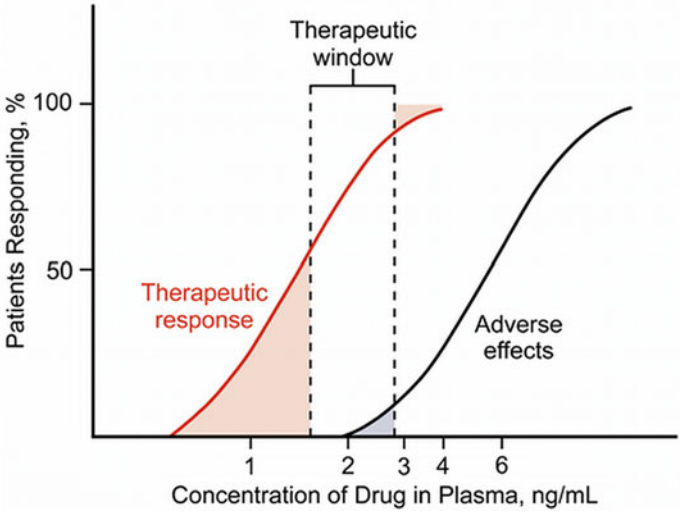

Fig. 2.1 The relation of the therapeutic window of drug concentration to the therapeutic and adverse effects in the patient population. The ordinate is linear; the abscissa is logarithmic [Adapted from Blumenthal DK, Garrison JC. Pharmacodynamics: molecular mechanisms of drug action. In: Brunton LL, Chabner BA, Knollmann BC, editors: Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, McGraw-Hill Medical, 2011, pp. 41–72. With permission from McGraw-Hill]

Pharmacodynamics also includes the ligand–receptor interactions that result in drug action. The *affinity* of a ligand or a drug for a receptor is the strength of the attraction for a receptor and ligand to bind; the affinity has a degree of *specificity.* Specificity may not be absolute for a given receptor, and a single drug may have affinity for several completely different types of receptor classes. In the case of diphenhydramine, affinity for the completely unrelated histamine and muscarine receptors is seen. By comparison, ondansetron has a greater specificity, showing affinity and selectivity for the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor subtype over other serotonin subtypes.

However, ligand affinity alone does not fully explain single drug action. After a ligand is bound to a receptor, the drug may act as an *agonist* (able to cause a full effect), a partial agonist (able to cause a submaximal effect), or an *antagonist* (occupying the receptor but not causing an effect). Although antagonists have affinity for a receptor and lack efficacy, their ability to act pharmacologically is to competitively or noncompetitively interfere with the action of an agonist.

An example of direct competitive antagonism is the interaction between nondepolarizing neuromuscular blocking drugs (NMBDs) and the acetylcholine receptors (nicotinic cholinergic receptors). NMBDs compete for receptor occupancy with acetylcholine and interfere with the binding of acetylcholine to the receptor, preventing a muscle contraction. An NMBD must occupy 75% to 80% of the receptors to cause clinically significant paralysis. The drug action is terminated through

metabolism over time, however; reversal of blockade can be facilitated indirectly with administration of an acetylcholinesterase inhibitor. These drugs bind with acetylcholinesterase and prevent the degradation of endogenous acetylcholine. This prevention increases the amount of acetylcholine available at the nicotinic receptors to compete with the neuromuscular blockers for binding. Because acetylcholine does not have absolute specificity for neuromuscular nicotinic receptors, a muscarinic antagonist needs to be coadministered to prevent parasympathetic adverse effects.

Receptor occupancy in an organ or enzyme system also assists in dictating drug action, and the effects are limited when either system reaches a saturation point. In this example, when a patient is paralyzed with an NMBD and demonstrates no muscle twitches when stimulated with a nerve stimulator, nearly all of the receptors are occupied. At this point, further administration of the NMBD does not confer additional efficacy. This clinical result is often referred to as a pharmacologic *ceiling effect*.

At full blockade, administration of a cholinesterase inhibitor is not effective because the degree of receptor occupation cannot be overcome by the endogenous increase in acetylcholine. Therefore, effective reversal of neuromuscular blockade is often achieved after the NMBD effect has begun to wane and the patient has at least one twitch return when stimulated with a train-of-four stimulus. Endogenous levels of acetylcholine as a result of acetylcholinesterase inhibition are then adequate to compete with the NMBD, thus allowing for muscle function recovery. Of note, the clinician needs to consider the duration of action of the administered NMBD when giving a reversal agent because re-paralysis is possible. If the duration of action of the reversal agent is shorter than that of the NMBD, the action of the NMBD continues after the cholinesterase inhibitor is no longer effective.

The effect of competitive antagonists can be overcome by increasing the concentration of the agonist, whereas the effect of noncompetitive antagonists cannot be overcome. Noncompetitive interactions are bound irreversibly or these ligands disassociate very slowly from the receptor (Fig. 2.2). Where irreversible interactions occur, a new receptor must be produced. Phenoxybenzamine is an example of a noncompetitive α-antagonist.

Receptors act as the mediators for many pharmacodynamic effects. The four main receptor families are ligand-gated ion channels, G protein-coupled receptors, enzyme-linked receptors, and intracellular receptors (Fig. 2.3). The majority of the receptors relevant in drug action are G protein–coupled receptors, including opioid (μ, κ, and δ subtypes), substance P, dopamine, serotonin, histamine$_1$ (H_1), cannabinoid, and muscarinic cholinergic and γ-aminobutyric acid$_B$ ($GABA_B$) receptors. The acetylcholine receptor (nicotinic cholinergic receptor) is an example of a ligand-gated ion channel, as are the N-methyl-D-aspartate (NMDA) and $GABA_A$ receptors. Enzyme-linked and intracellular receptors are less commonly drug targets. Enzyme-linked receptors include the natriuretic peptide receptor and epidermal growth factor receptors. Estrogen, mineralocorticoid, and thyroid hormone receptors are examples of intracellular receptors.

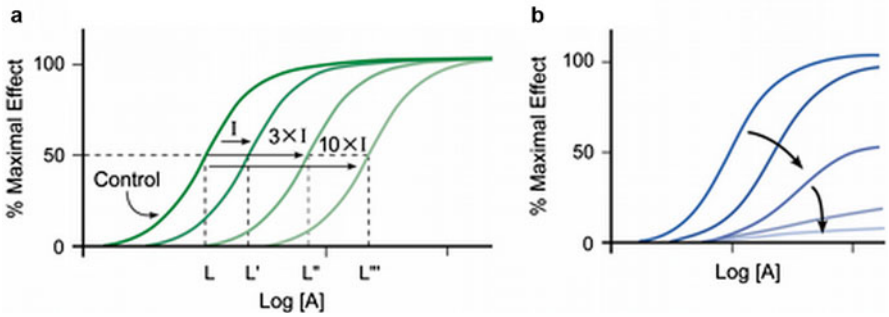

Fig. 2.2 Mechanisms of receptor antagonism. A, Competitive antagonism occurs when agonist A and antagonist I compete for the same binding site on the receptor. Response curves for the agonist are shifted to the right in a concentration-related manner by the antagonist, such that the EC50 (the concentration of drug that gives half maximal effect) for the agonist increases (ie, L vs L′, L", and L′′′) with the concentration of the antagonist. B, If the antagonist binds to the same site as the agonist but does so irreversibly or pseudoirreversibly (slow dissociation but no covalent bond), it causes a shift of the dose-response curve to the right, with further depression of the maximal response [Adapted from Blumenthal DK, Garrison JC. Pharmacodynamics: molecular mechanisms of drug action. In: Brunton LL, Chabner BA, Knollmann BC, (Eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, McGraw-Hill Medical, 2011, pp. 41-72. With permission from McGraw-Hill]

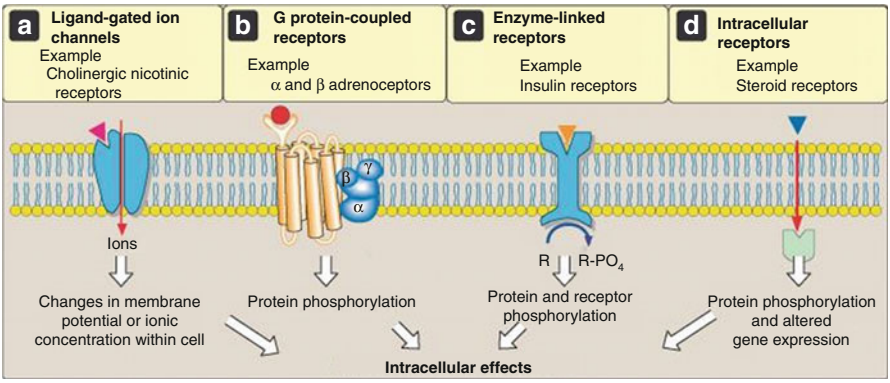

Fig. 2.3 Transmembrane signaling mechanisms. A, Ligand binds to extracellular domain of a ligand-gated channel. B, Ligand binds to a domain of a serpentine receptor, which is coupled to a G protein. C, Ligand binds to the extracellular domain of a receptor that activates a kinase system. D, Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor [Adapted from Finkel R, Clark MA, Cubeddu LX, (Eds.). Pharmacology, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2009. With permission from Wolters Kluwer Health]

Tolerance is the development, over time, of a resistance to the effects of a drug. An increased amount of the drug must be administered to achieve the same level of effect that was achieved earlier with less drug. Pharmacodynamically, this resistance may be due in part to receptor re-regulation. Continuous exposure to drugs may

cause receptor upregulation or downregulation and result in a change of overall receptor density. Tolerance may be to a single agent or to other drugs of a similar class or with a similar mechanism—a phenomenon often referred to as *cross-tolerance*. Cross-tolerance between two different drugs may be complete (ie, similar in degree of tolerance) or incomplete (ie, tolerance is reduced in degree).

An important point of consideration is that tolerance may also build up toward one effect of a drug and not another effect. As the dose is increased to achieve the same desired effect, other effects may increase in intensity. A classic example is opioid use. Persons taking opioids on a long-term basis eventually have tolerance to the medication's analgesic, or pain-relieving, effect, thereby requiring increased doses over time. However, tolerance does not develop to all the opioid effects, for example, adverse effects of opioids include constipation, and tolerance to opioid-induced constipation does not develop as it does toward the analgesic effect.

Tolerance is not the same as *addiction* or *dependence*. Dependence is physiological and often seen on cessation of a drug, eliciting a withdrawal syndrome. Opioids can cause both tolerance and dependence and, given enough time, these effects are expected pharmacologically. Addiction, however, is a psychological phenomenon and the drug becomes the focus of behavior. Although a patient may present with tolerance, dependence, and addiction to an opioid, addiction is not a regularly expected pharmacologic outcome in pain management.

Tolerance also should be differentiated from *tachyphylaxis.* Although tolerance develops gradually during long-term administration, tachyphylaxis is a rapid decrease in drug effect that may begin with the initial drug administration. Transdermal nitroglycerin is an example of a drug that undergoes tachyphylaxis and requires drug-free intervals because of the decrease in effect.

Pharmacodynamic interactions occur when two or more drugs are given concomitantly. An *additive* interaction occurs when the combined effect of two drugs equals the sum of their individual effects. By comparison, *synergy* is an important concept in pharmacodynamics and in understanding drug interactions. These interactions may occur unwittingly or drug properties may be taken advantage of to increase a desired effect. Synergy occurs when two drugs are combined in therapy and produce a pharmacologic effect greater than the sum of their individual effects. The degree of respiratory depression observed as a result of concomitant administration of midazolam and fentanyl is an adverse effect that demonstrates synergism. In contrast, the synergistic effect on sedation is desirable in many situations. When considering hypnosis and immobility in anesthesia, the clinician needs to be aware that drug combinations that act at the same receptor are likely to act in an additive manner; drugs that act at different receptors are more likely to act synergistically.[1]

Drug combinations that result in antagonistic interactions also deserve consideration. *Antagonism* occurs when the combined effect of two drugs is less than the

sum of their individual effects. Commonly, when antagonism is considered, one drug is administered to decrease the effect of another, as in the case of naloxone reversal of an opiate. However, antagonism also occurs when the effect of two drugs administered together is greater than the effect of either drug alone but is less than the projected additive effect of each drug. This response is often described as an *infra-additive interaction*. The combination of isoflurane and nitrous oxide results in an infra-additive interaction since the combination produces less than an additive effect on hypnosis but more than the effect of either agent alone.[1]

Knowledge of the individual types of interactions (synergy, additive, or antagonistic) enables complex interactions to be broken down and understood in a more thorough level. Such improved understanding may be used to recognize and, hopefully, to predict and prevent adverse drug interactions.

Reference

1. Hendrickx JF, Eger 2nd EI, Sonner JM, et al. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg. 2008;107:494–506.