Pharmacology

Lecture 1

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed **pharmacodynamic** processes. 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.

Pharmacokinetics

• **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

• **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

• **Metabolism:** Third, the drug may be biotransformed by metabolism by the liver or other tissues.

• **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, the dose, the frequency, and the duration of treatment.

Routes of drugs administration:

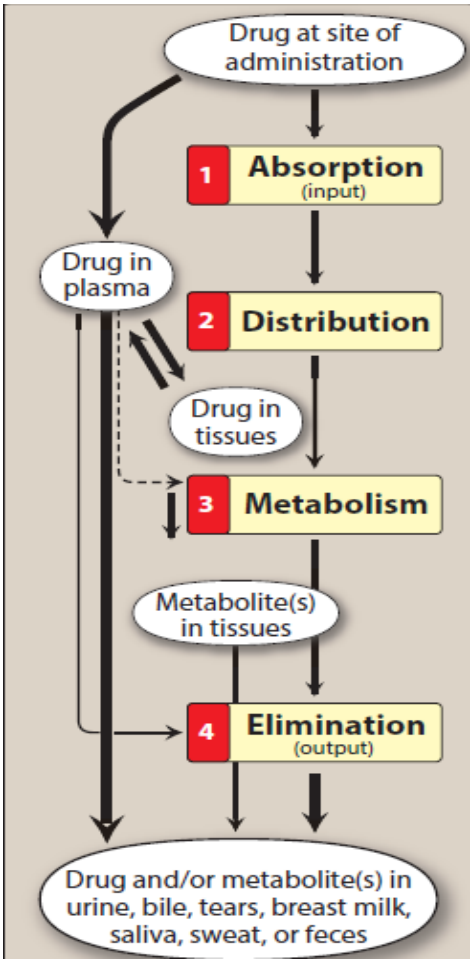
A. Enteral:

Enteral administration (administering a drug by mouth) is the safest and most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual), or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal.

However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

Placement under the tongue allows a drug to diffuse into the capillary network and enter the systemic circulation directly.



Sublingual administration has several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first pass metabolism.

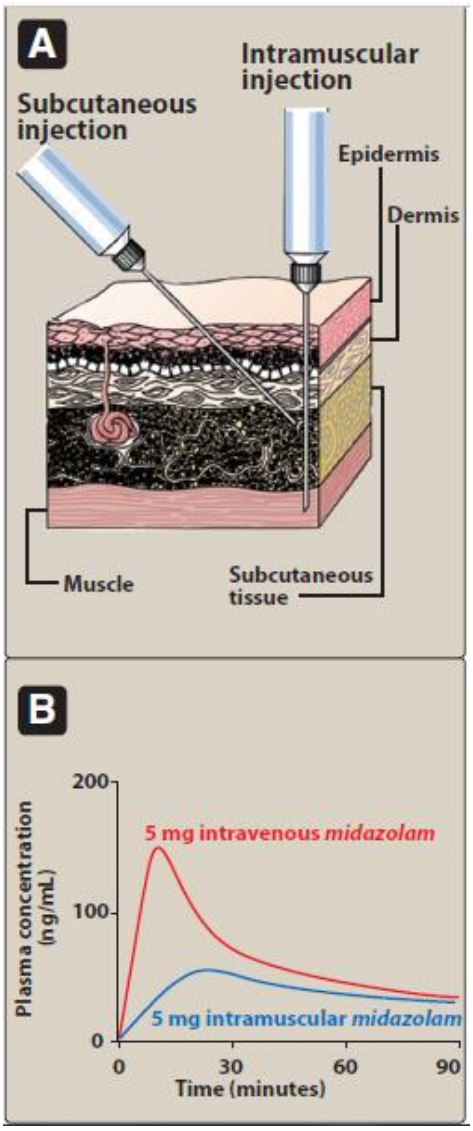
The buccal route (between the cheek and gum) is similar to the sublingual route.

B. Parenteral:

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used if a patient is unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action.

In addition, parenteral routes have the highest bioavailability and are not subject to first-pass metabolism or the harsh GI environment. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these routes of administration are irreversible and may cause pain, fear, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous.

1. Intravenous (IV): IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally.
IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period of time, resulting in lower peak plasma concentrations and an increased duration of circulating drug levels. IV administration is advantageous for drugs that cause irritation when administered via other routes, because the substance is rapidly diluted by the blood.
IV injection may inadvertently introduce infections through contamination at the site of injection. It may also precipitate blood constituents, induce hemolysis, or cause other adverse reactions if the medication is delivered too rapidly and high concentrations are reached too quickly. Therefore, patients must be carefully monitored for drug reactions, and the rate of infusion must be carefully controlled.



2. Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of the drug in a nonaqueous vehicle such as polyethylene glycol.

3. Subcutaneous (SC): Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.
Drugs commonly administered via the subcutaneous route include *insulin* and *heparin*.

C. <u>Other:</u>

1. Oral inhalation: Inhalation routes, both oral and nasal, provide rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as those with IV bolus.

Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders (such as asthma or chronic obstructive pulmonary disease), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects.

2. Nasal inhalation: This route involves administration of drugs directly into the nose. Examples of agents include nasal decongestants.

3. Intrathecal/intraventricular: The blood–brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.

4. Topical: Topical application is used when a local effect of the drug is desired.

5. Transdermal: This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug. This route is most often used for the sustained delivery of drugs, such as the antianginal drug *nitroglycerin*.

6. Rectal: Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious.

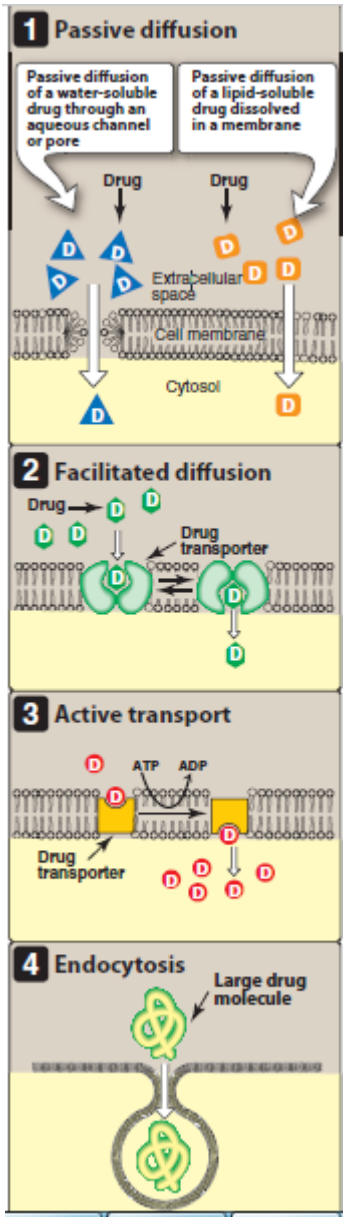
Absorption of drugs:

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

B. Factors influencing absorption



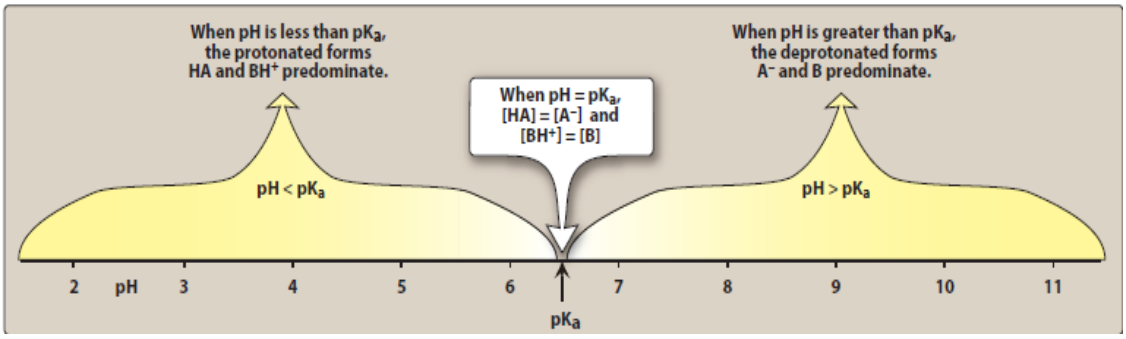
1. Effect of pH on drug absorption:

Most drugs are either weak acids or weak bases. A drug passes through membranes more readily if it is uncharged. Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pKa .

2. Blood flow to the absorption site: The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach.

3. Total surface area available for absorption: With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4. Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.



5. Expression of P-glycoprotein:

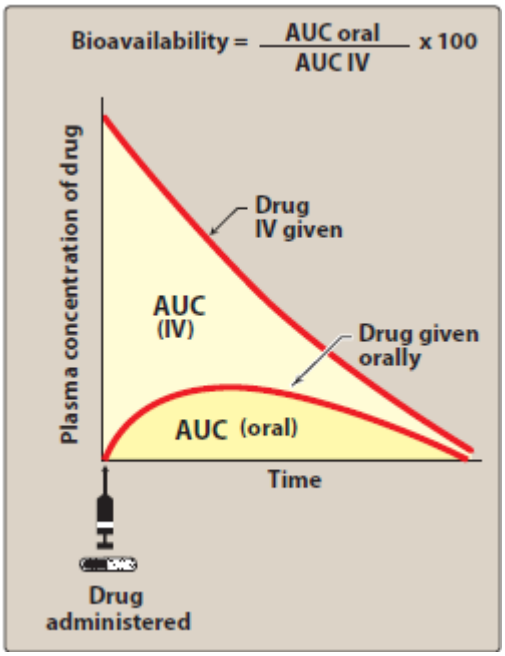
P-glycoprotein is a trans-membrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.
It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it "pumps" drugs out of the cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

C. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.

In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to the chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

Drug distribution:



Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

For drugs administered IV, absorption is not a factor, and the initial phase (from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues. The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug.

Volume of distribution:

The apparent volume of distribution, V_d, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

The fact that drug clearance is usually a first-order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time. The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of V_d as

$$V_d = \frac{\text{Dose}}{C_0}$$

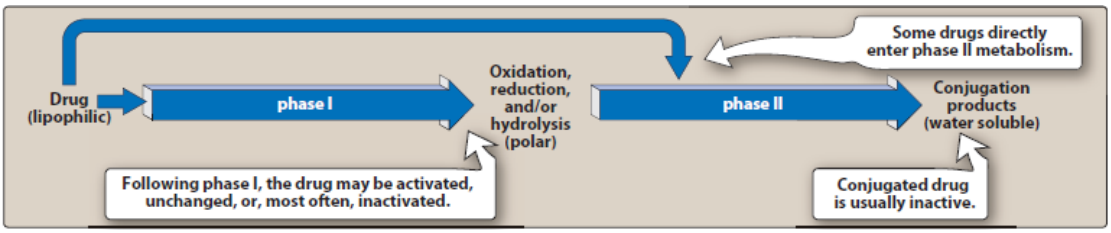
For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L, then V_d = 10 mg/1 mg/L = 10 L.

Drug clearance through metabolism:

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary elimination. Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug present is eliminated in a given unit of time.

Most drugs are eliminated according to first-order kinetics, although some, such as *aspirin* in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time.

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.



Drug clearance through kidney:

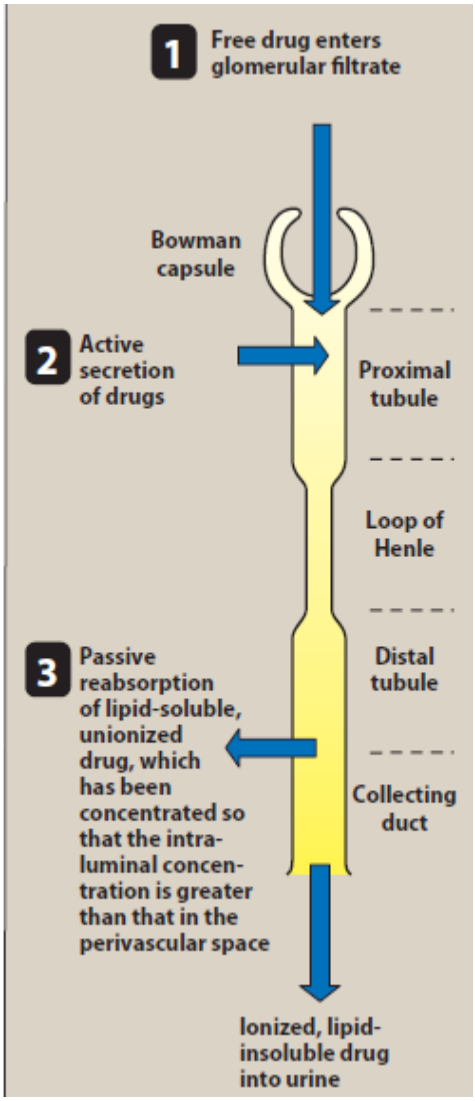
Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes, the most important being elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

Elimination of drugs via the kidneys into urine involves the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1. Glomerular filtration:

Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate. The glomerular filtration rate (GFR) is normally about 125 mL/min but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate.

However, variations in GFR and protein binding of drugs do affect this process.



2. Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for

anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of thesetransport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system.

3. Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation.

Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.” For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate*, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

Pharmacology

Lecture 3

Drug–Receptor Interactions and Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors (that is, specialized target macromolecules) present on the cell surface or within the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction.

Most drug targets (receptors) are protein molecules. Even general anesthetics, which were long thought to produce their effects by an interaction with membrane lipid, now appear to interact mainly with membrane proteins.

All rules need exceptions, and many antimicrobial and antitumor drugs, as well as mutagenic and carcinogenic agents, interact directly with DNA rather than protein.

Types of Receptors:

Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists. However, the richest sources of therapeutically relevant pharmacologic receptors are proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families:

1) ligand-gated ion channels.
2) G protein- coupled receptors.
3) enzyme-linked receptors.
4) intracellular receptors .

The type of receptor a ligand interacts with depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface (Figures 1 A, B, C). In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 1 D).

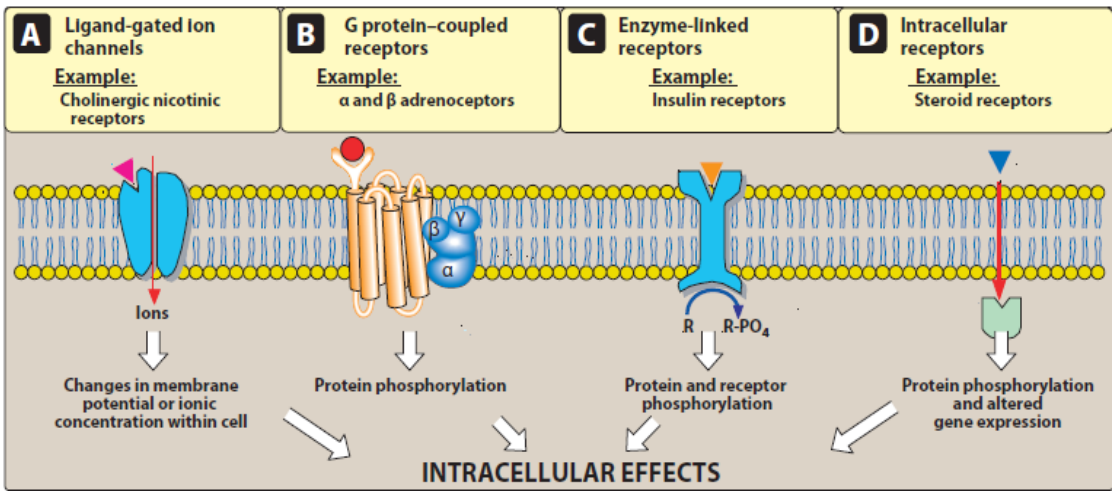


Figure 1: *Transmembrane signaling mechanisms.*

1. **Transmembrane ligand-gated ion channels:**

The extracellular portion of ligand-gated ion channels usually contains the ligand binding site. This site regulates the shape of the pore through which ions can flow across cell membranes (Figure 1A). The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron or contraction in skeletal muscle. On the other hand, agonist stimulation of the γ-aminobutyric acid (GABA) receptor increases chloride influx and hyperpolarization of neurons. Voltage-gated ion channels may also possess ligand-binding sites that can regulate channel function. For example, local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

2. **Transmembrane G protein–coupled receptors:**

The extracellular domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule. There are many kinds of G proteins (for example, Gs, Gi, and Gq), but they all are composed of three protein subunits. The α subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane Figure 2). Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of

the α-GTP complex from the βγ complex. These two complexes can then interact with other cellular effectors, usually an enzyme, a protein, or an ion channel, that are responsible for further actions within the cell. These responses usually last several seconds to minutes.

Sometimes, the activated effectors produce second messengers that further activate other effectors in the cell, causing a signal cascade effect.

A common effector, activated by Gs and inhibited by Gi, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). Gq activates phospholipase C, generating two other second messengers: inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). DAG and cAMP activate different protein kinases within the cell, leading to a myriad of physiological effects. IP3 regulates intracellular free calcium concentrations, as well as some protein kinases.

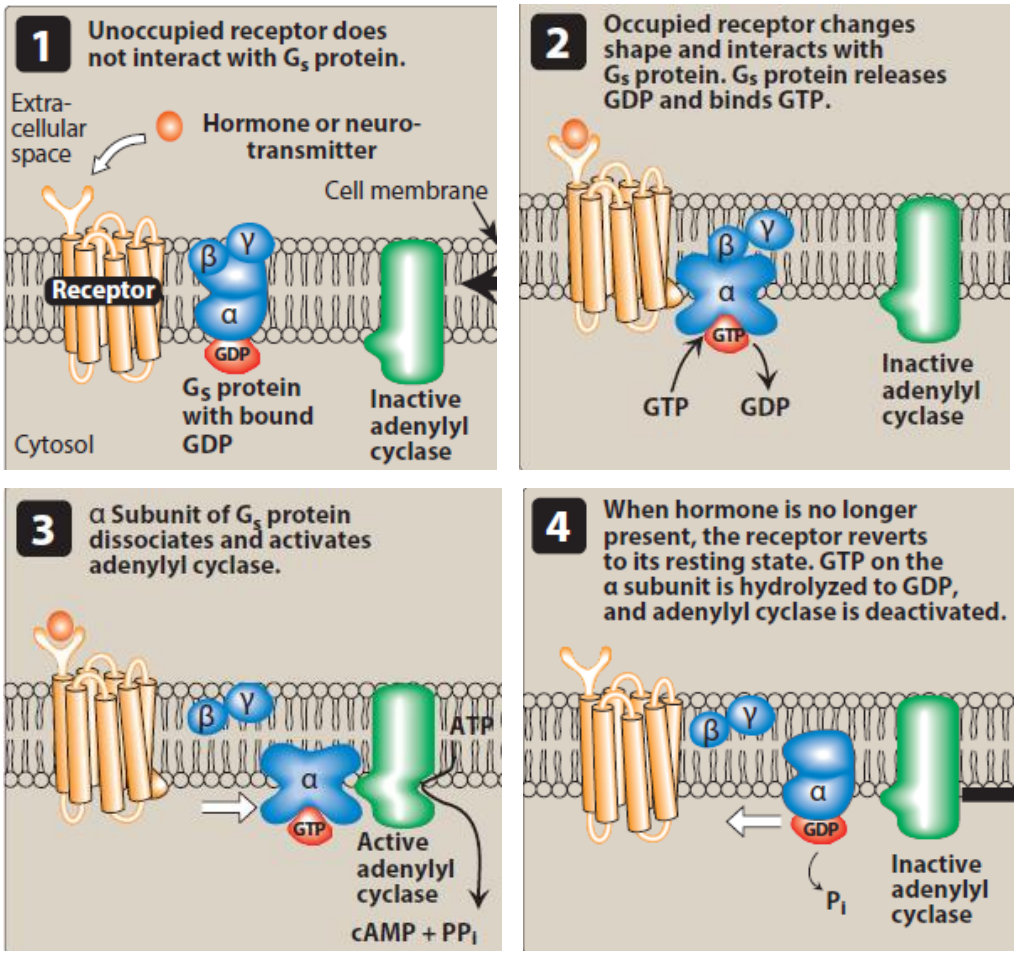


Figure 2: *The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase.*

3. **Enzyme-linked receptors:**

This family of receptors consists of a protein that may form dimers or multisubunit complexes. When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function (Figure 3). This response lasts on the order of minutes to hours. The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) possess tyrosine kinase activity as part of their structure. The activated receptor phosphorylates tyrosine residues on itself and then other specific proteins (Figure 3). Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates other peptides or proteins that subsequently activate other important cellular signals. This cascade of activations results in a multiplication of the initial signal, much like that with G protein–coupled receptors.

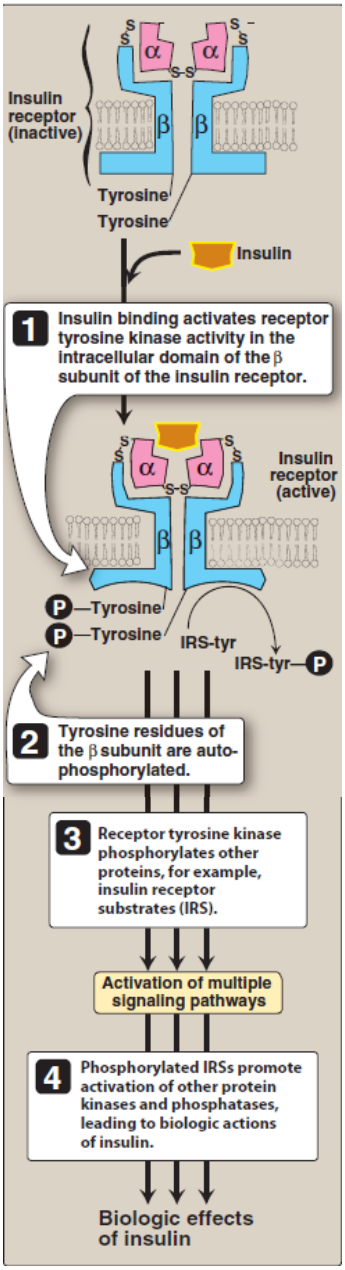


Figure 3: *Insulin receptor.*

4. **Intracellular receptors:**

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor (Figure 2.5). In order to move across the target cell membrane, the ligand must have sufficient lipid solubility. The primary targets of these ligand– receptor complexes are transcription factors in the cell nucleus.

Binding of the ligand with its receptor generally activates the receptor via dissociation from a variety of binding proteins. The activated ligand–receptor complex then translocates to the nucleus, where it often dimerizes before binding to transcription factors that regulate gene expression. The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins. The time course of activation and response of these receptors is on the order of hours to days. For example, steroid hormones exert their action on target cells via intracellular receptors. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel*, the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim*, and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin*.

Pharmacology

Lecture 4

Drug–Receptor Interactions and Pharmacodynamics

Dose-Response Relationship:

Occupation of a receptor by a drug molecule may or may not result in *activation* of the receptor. By activation, we mean that the receptor is affected by the bound molecule in such a way as to alter the receptor's behavior towards the cell and elicit a tissue response.

Binding and activation represent two distinct steps in the generation of the receptor-mediated response by an agonist (Fig. 1). If a drug binds to the receptor without causing activation and thereby prevents the agonist from binding, it is termed a *receptor antagonist*. The tendency of a drug to bind to the receptors is governed by its *affinity*, whereas the tendency for it, once bound, to activate the receptor is denoted by its *efficacy*.

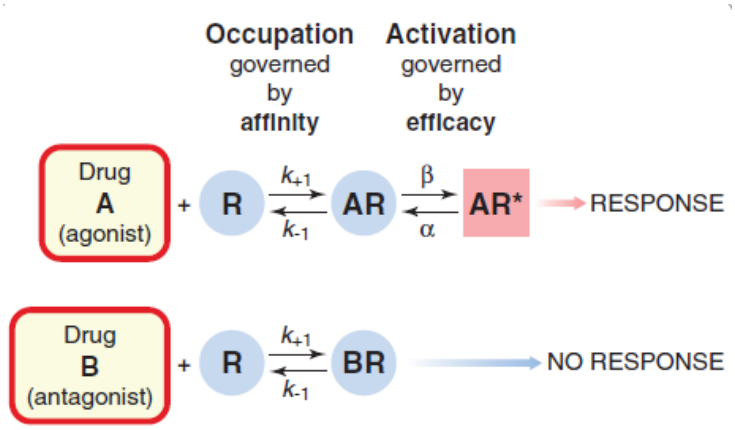


Figure 1: *The distinction between drug binding and receptor activation. Ligand A is an agonist, because when it is bound, the receptor (R) tends to become activated, whereas ligand B is an antagonist, because binding does not lead to activation. It is important to realise that for most drugs, binding and activation are reversible, dynamic processes. The rate constants k+1, k−1, α and β for the binding, unbinding and activation steps vary between drugs. For an antagonist, which does not activate the receptor, β = 0.*

Drugs of high potency generally have a high affinity for the receptors and thus occupy a significant proportion of the receptors even at low concentrations. Agonists also possess significant efficacy, whereas antagonists, in the simplest case, have zero efficacy. Drugs with intermediate levels of efficacy, such that even when 100% of the receptors are occupied the tissue response is submaximal, are known as *partial agonists*, to distinguish them from *full agonists*, the efficacy of which is sufficient that they can elicit a maximal tissue response.

Agonist drugs mimic the action of the original endogenous ligand for the receptor (for example, *isoproterenol* mimics norepinephrine on β1 receptors of the heart). The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

THE BINDING OF DRUGS TO RECEPTORS

The *binding curve* (Fig. 2 A, B) defines the relationship between concentration and the amount of drug bound as well as the *binding capacity* (B_{max}), representing the density of receptors in the tissue.

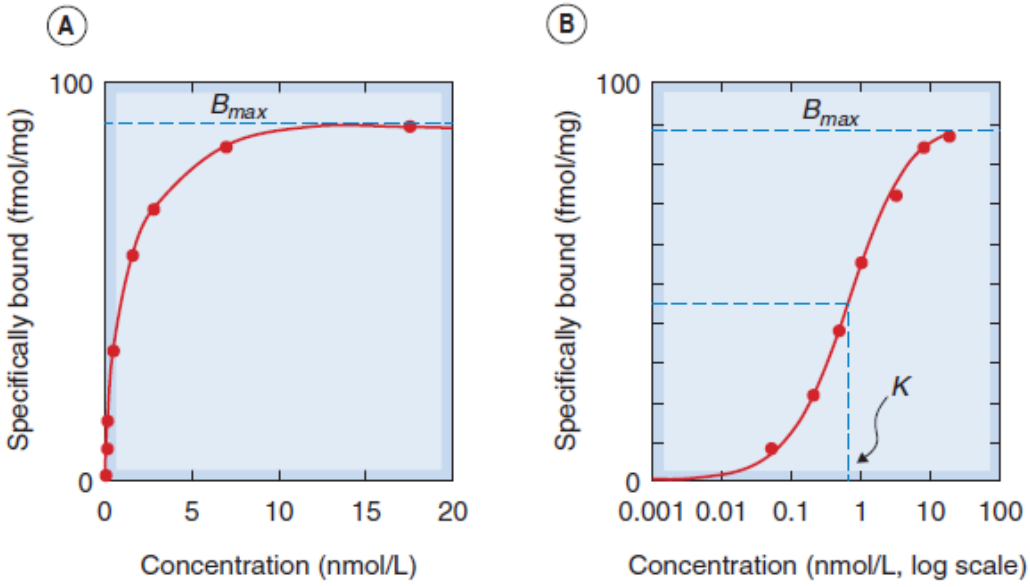


Figure 2: Measurement of receptor binding (β adrenoceptors in cardiac cell membranes). [A] Specific binding plotted against concentration. The curve is a rectangular hyperbola. [B] Specific binding as in [A] plotted against the concentration on a log scale. The sigmoid curve is a *logistic curve* representing the logarithmic scaling of the rectangular hyperbola plotted in panel [A] from which the binding parameters *K* and *B*max can be determined.

A. Graded dose–response relations

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve that has the general shape depicted in Figure 3A. The curve can be

described as a rectangular hyperbola, which is a familiar curve in biology because it can be applied to diverse biological events, such as enzymatic activity, and responses to pharmacologic agents. Two important properties of drugs, potency and efficacy, can be determined by graded dose–response curves.

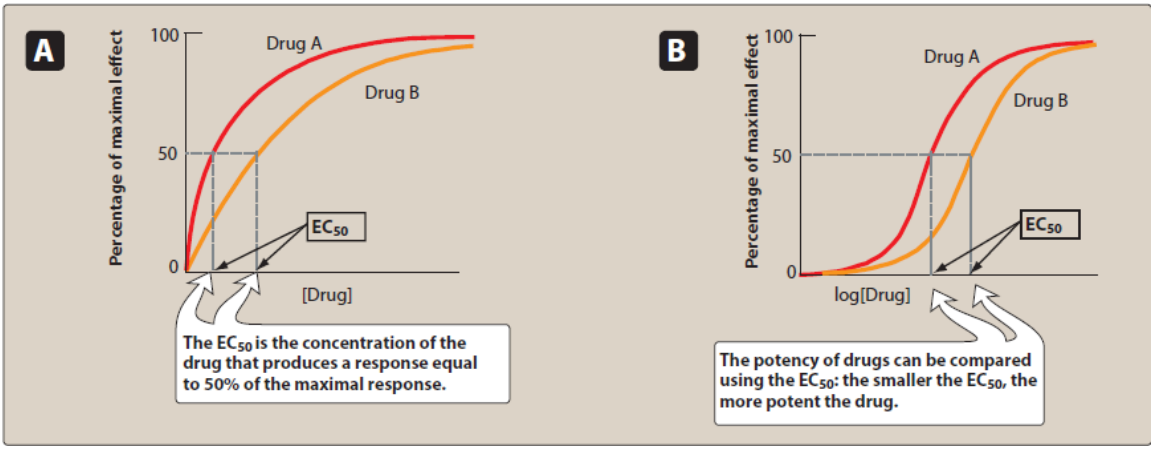


Figure 3: *The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semilogarithmic plot of the same data. EC50 = drug dose causing 50% of maximal response.*

1. **Potency:** Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. The concentration of drug producing 50% of the maximum effect (EC_{50}) is usually used to determine potency. In Figure 3, the EC_{50} for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect. Therapeutic preparations of drugs reflect their potency. For example, *candesartan* and *irbesartan* are angiotensin receptor blockers that are used to treat hypertension. The therapeutic dose range for *candesartan* is 4 to 32 mg, as compared to 75 to 300 mg for *irbesartan.* Therefore, *candesartan* is more potent than is *irbesartan* (it has a lower EC_{50} value, similar to Drug A in Figure 3). Since the range of drug concentrations (from 1% to 99% of the maximal response) usually spans several orders of magnitude, semilogarithmic plots are used so that the complete range of doses can be graphed. As shown in Figure 3B, the curves become sigmoidal in shape, which simplifies the interpretation of the dose– response curve.
2. **Efficacy:** Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and

the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response).

Maximal efficacy of a drug (E_{max}) assumes that all receptors are occupied by the drug, and no increase in response is observed if a higher concentration of drug is obtained. Therefore, the maximal response differs between full and partial agonists, even when 100% of the receptors are occupied by the drug. Similarly, even though an antagonist occupies 100% of the receptor sites, no receptor activation results and E_{max} is zero. Efficacy is a more clinically useful characteristic than is drug potency, since a drug with greater efficacy is more therapeutically beneficial than is one that is more potent. Figure 4 shows the response to drugs of differing potency and efficacy.

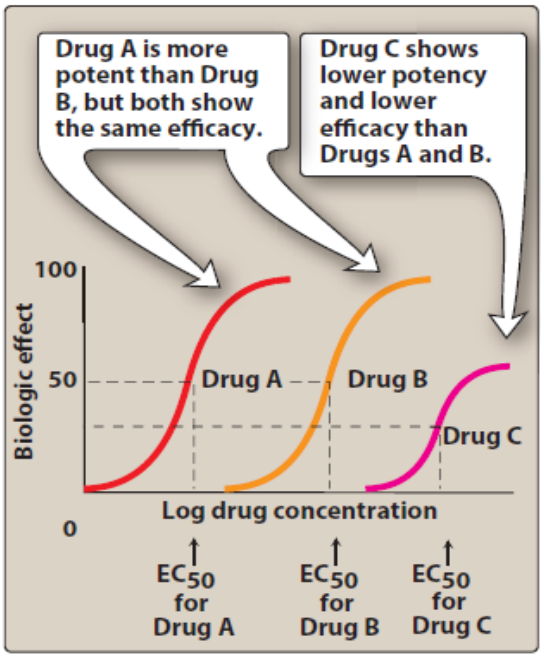


Figure 4: *Typical dose–response curve for drugs showing differences in potency and efficacy. EC50 = drug dose that shows 50% of maximal response.*

Thus, even if the concentration–effect curves, as in Figure 3B, looks just like a facsimile of the binding curve (Fig. 2B), it cannot be used directly to determine the affinity of the agonist for the receptors.

Spare receptors:

In the studying the actions of acetylcholine analogues in isolated tissues, found that many full agonists were capable of eliciting maximal responses at very low occupancies, often less than 1%. This means that the mechanism linking the response to receptor occupancy has a substantial reserve capacity. Such systems may be said to possess *spare receptors*, or a receptor reserve

Intrinsic Activity:

As mentioned above, an agonist binds to a receptor and produces a biologic response based on the concentration of the agonist and the fraction of activated receptors. The intrinsic activity of a drug determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting Emax values.

A. Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist (Figure 5). Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one. All full agonists for a receptor population should produce the same E_{max}. For example, *phenylephrine* is a full agonist at α1-adrenoceptors, because it produces the same Emax as does the endogenous ligand, norepinephrine.

Upon binding to α1-adrenoceptors on vascular smooth muscle, *phenylephrine* stabilizes the receptor in its active state. This leads to the mobilization of intracellular Ca^{2+}, causing interaction of actin and myosin filaments and shortening of the muscle cells. The diameter of the arteriole decreases, causing an increase in resistance to blood flow through the vessel and an increase in blood pressure. As this brief description illustrates, an agonist may have many measurable effects, including actions on intracellular molecules, cells, tissues, and intact organisms.

All of these actions are attributable to interaction of the drug with the receptor. For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.

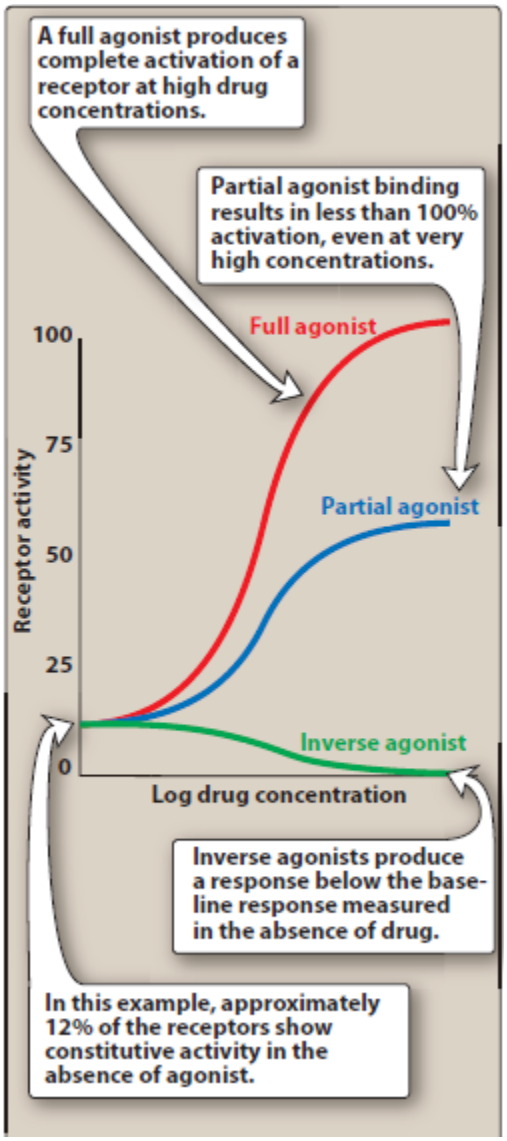


Figure 5: *Effects of full agonists, partial agonists, and inverse agonists on receptor activity.*

B. Partial agonists

Partial agonists have intrinsic activities greater than zero but less than one (Figure 5). Even if all the receptors are occupied, partial agonists cannot produce the same E_{max} as a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. When a receptor is exposed to both a partial agonist

and a full agonist, the partial agonist may act as an antagonist of the full agonist. Consider what would happen to the E_{max} of a receptor saturated with an agonist in the presence of increasing concentrations of a partial agonist (Figure 6). As the number of receptors occupied by the partial agonist increases, the E_{max} would decrease until it reached the E_{max} of the partial agonist. This potential of partial agonists to act as both an agonist and antagonist may be therapeutically utilized. For 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, with a small risk of causing extrapyramidal adverse effects.

C. Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation. However, some receptors show a spontaneous conversion from R to R* in the absence of an agonist (constitutive activation). Inverse agonists, unlike full agonists, stabilize the inactive R form and cause R* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug (Figure 5). Thus, inverse agonists have an intrinsic activity less than zero, reverse the activity of receptors, and exert the opposite pharmacological effect

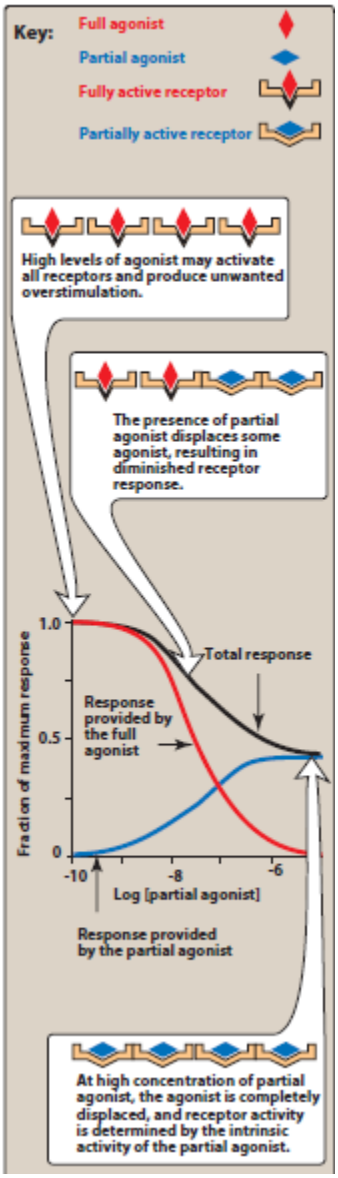


Figure 6: Effects of partial agonists.

Pharmacology

Lecture 5

Drug–Receptor Interactions and Pharmacodynamics

Antagonist:

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect in the absence of an agonist but can decrease the effect of an agonist when present.

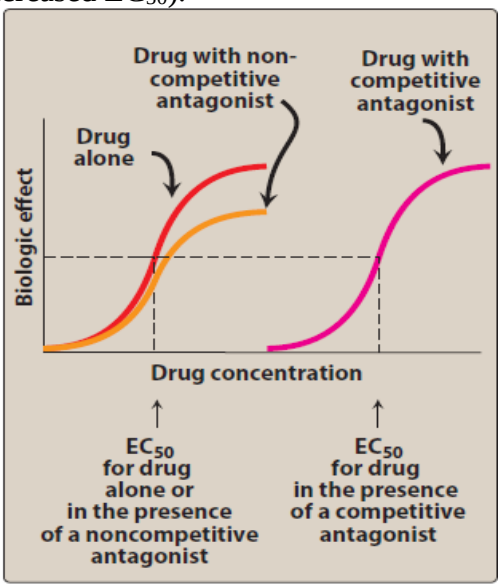
Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

Receptor antagonists bind to receptors but do not activate them; the primary action of antagonists is to reduce the effects of agonists (other drugs or endogenous regulatory molecules) that normally activate receptors. While antagonists are traditionally thought to have no functional effect in the absence of an agonist, some antagonists exhibit "inverse agonist" activity (see lecture 4) because they also reduce receptor activity below basal levels observed in the absence of any agonist at all. Antagonist drugs are further divided into two classes depending on whether or not they act *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; that is, the E_{max} for the agonist remains the same for any fixed concentration of antagonist (Figure 1). Because the antagonism is competitive, the presence of antagonist increases the agonist concentration required for a given degree of response, and so the agonist concentration-effect curve is shifted to the right (increased EC_{50}).

The concentration of an agonist required to produce a given effect in the presence of a fixed concentration of competitive antagonist is greater than the agonist concentration required producing the same effect in the absence of the antagonist.

The ratio of these two agonist concentrations (dose ratio) is related to the dissociation constant (Ki) of the antagonist.



The salient features of competitive antagonism are:

- Shift of the agonist log concentration–effect curve to the right, without change of slope or maximum (i.e. antagonism can be overcome by increasing the concentration of the agonist).
- Linear relationship between agonist dose ratio and antagonist concentration
- Evidence of competition from binding studies.

Competitive antagonism is the most direct mechanism by which one drug can reduce the effect of another (or of an endogenous mediator).

The actions of a **noncompetitive antagonist** are different because, once a receptor is bound by such a drug; agonists cannot surmount the inhibitory effect irrespective of their concentration.

In many cases, noncompetitive antagonists bind to the receptor in an **irreversible** or nearly irreversible fashion, sometimes by forming a covalent bond with the receptor. After occupancy of some proportion of receptors by such an antagonist, the number of remaining unoccupied receptors may be too low for the agonist (even at high concentrations) to elicit a response comparable to the previous maximal response.

If spare receptors are present, however, a lower dose of an irreversible antagonist may leave enough receptors unoccupied to allow achievement of maximum response to agonist, although a higher agonist concentration will be required (figure 2).

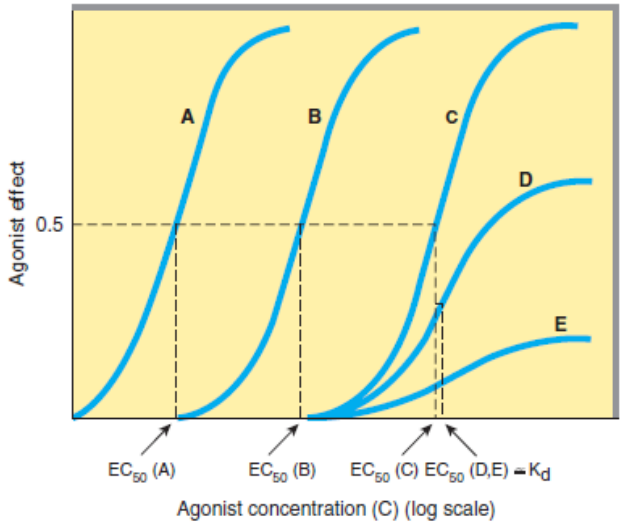


Figure 2: Logarithmic transformation of the dose axis and experimental demonstration of spare receptors, using different concentration of an irreversible antagonist. Curve **A** shows agonist response in the absence of antagonist. After treatment with a low concentration of antagonist (curve **B**), the curve is shifted to the right. Maximal responsiveness is preserved, however, because the remaining available receptors are still in excess of the number required. In curve **C,** produced after treatment with a larger concentration of antagonist, the available receptors are no longer "spare"; instead, they are just sufficient to mediate an undiminished maximal response. Still higher concentrations of antagonist (curves **D** and **E**) reduce the number of available receptors to the point that maximal response is diminished. The apparent EC_{50} of the agonist in curves **D** and **E** may approximate the Kd that characterizes the binding affinity of the agonist for the receptor.

Antagonists can function noncompetitively in a different way; that is, by binding to a site on the receptor protein separate from the agonist binding site; in this way, the drug can modify receptor activity without blocking agonist binding (Figure 3C and D).

Although these drugs act noncompetitively, their actions are often reversible. Such drugs are called *negative allosteric modulators* because they act by binding to a different (ie, "allosteric") site on the receptor relative to the classical ("orthosteric") site bound by the agonist. Not all allosteric modulators act as antagonists; some bind an allosteric site but, instead of inhibiting receptor activation, potentiate it. For example, benzodiazepines are considered *positive allosteric modulators* because they bind noncompetitively to ion channels activated by the neurotransmitter γ-aminobutyric acid (GABA), thereby enhancing the net activating effect of GABA on channel conductance.

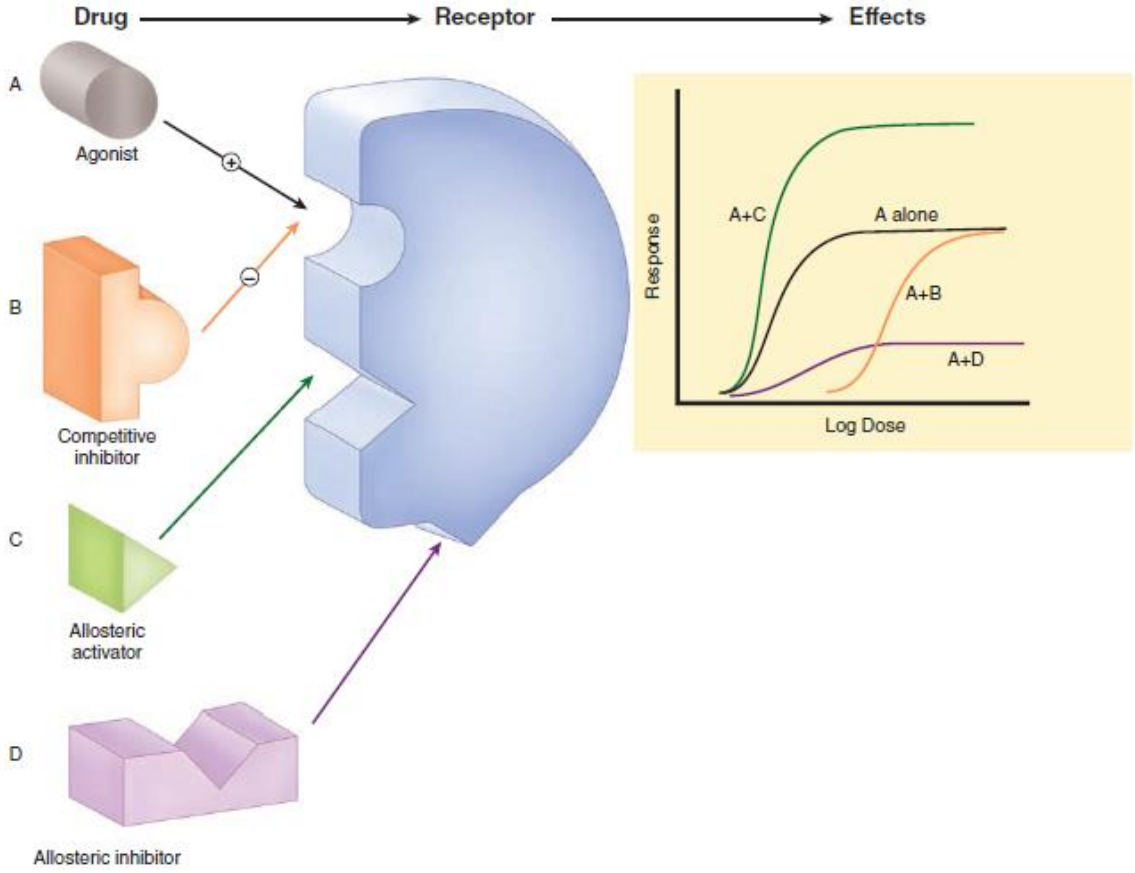


Figure 3: *Drugs may interact with receptors in several ways. The effects resulting from these interactions are diagrammed in the dose-response curves at the right. Drugs that alter the agonist (**A**) response may activate the agonist binding site, compete with the agonist (competitive inhibitors, **B**), or act at separate (allosteric) sites, increasing (**C**) or decreasing (**D**) the response to the agonist. Allosteric activators (**C**) may increase the efficacy of the agonist or its binding affinity. The curve shown reflects an increase in efficacy; an increase in affinity would result in a leftward shift of the curve.*

Functional antagonism: An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the functional antagonism by epinephrine to histamine-induced bronchoconstriction. Histamine binds to H1 histamine receptors on bronchial smooth muscle, causing

bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as "physiologic antagonism."

Quantal Dose-Response Curve:

Another important dose–response relationship is that between the dose of the drug and the proportion of a population that responds to it. These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not. Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response as the point at which a response occurs or not. For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug *atenolol.* A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure. Quantal dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose–response curves, and the ED_{50} is the drug dose that causes a therapeutic response in half of the population.

A. Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

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

The TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

Clinical usefulness of the therapeutic index

The TI of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses.

Although high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases.

In these cases, the risk of experiencing side effects is not as great as the risk of leaving the disease untreated. Figure 4 shows the responses to *warfarin*, an oral anticoagulant with a low therapeutic index, and *penicillin,* an antimicrobial drug with a large therapeutic index.

Warfarin (example of a drug with a small therapeutic index):

As the dose of *warfarin* is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond (Figure 4A). However, at higher doses of *warfarin*, anticoagulation resulting in hemorrhage occurs in a small percent of patients. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects.

Penicillin (example of a drug with a large therapeutic index):

For drugs such as *penicillin* (Figure 4B), it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse side effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

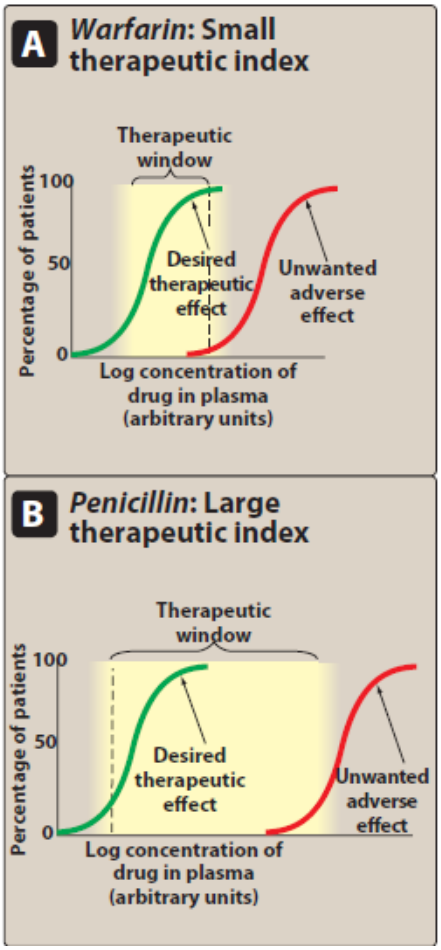


Figure 4: Cumulative percentage of patients responding to plasma levels of *warfarin* and *penicillin.*

Key Note:

• Drugs acting on receptors may be *agonists* or *antagonists*.
• Agonists initiate changes in cell function, producing effects of various types; antagonists bind to receptors without initiating such changes.
• Agonist potency depends on two parameters: *affinity* (i.e. tendency to bind to receptors) and *efficacy* (i.e. ability, once bound, to initiate changes that lead to effects).
• For antagonists, efficacy is zero.
• *Full agonists* (which can produce maximal effects) have high efficacy; *partial agonists* (which can produce only submaximal effects) have intermediate efficacy.
• *Inverse agonists* show selectivity for the resting state of the receptor, this being of significance only in situations where the receptors show *constitutive activity*.
• *Allosteric modulators* bind to sites on the receptor other than the agonist binding site and can modify agonist activity.

Pharmacology

Lecture 6

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 **hyporeactive** or **hyperreactive** to 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.) 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 (Desensitization).**

Even before administering the first dose of a drug, the prescriber should consider factors that may help in predicting the direction and extent of possible variations in responsiveness. These include the propensity of a particular drug to produce tolerance or tachyphylaxis as well as the effects of age, sex, body size, disease state, genetic factors, and simultaneous administration of other drugs.

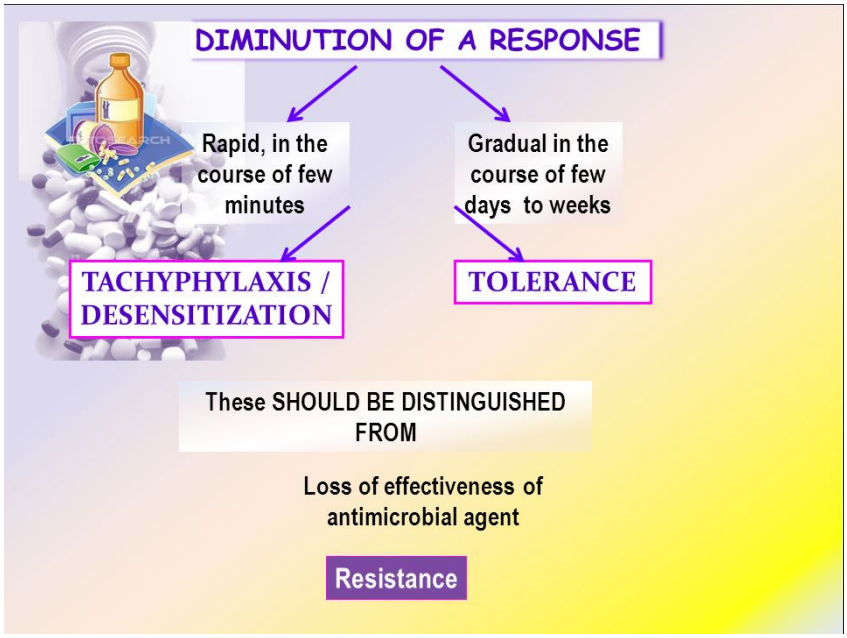
The term *tolerance* is conventionally used to describe a more gradual decrease in responsiveness to a drug, taking hours, days or weeks to develop, but the distinction is not a sharp one. *Drug resistance* is a term used to describe the loss of effectiveness of antimicrobial or antitumor drugs. Many different mechanisms can give rise to these phenomena. They include:

- Change in receptors
- Translocation of receptors
- Exhaustion of mediators
- increased metabolic degradation of the drug
- Physiological adaptation
- Active extrusion of drug from cells (mainly relevant in cancer chemotherapy)

Change in Receptors:

Among receptors directly coupled to ion channels, desensitization is often rapid and pronounced. At the neuromuscular junction, the desensitized state is caused by a conformational change in the receptor, resulting in tight binding of the agonist molecule without the opening of the ionic channel. Phosphorylation of intracellular regions of the receptor protein is a second, slower mechanism by which ion channels become desensitized.

Most G protein-coupled receptors also show desensitization. Phosphorylation of the receptor interferes with its ability to activate second messenger cascades, although it can still bind the agonist molecule. This type of desensitization usually takes seconds to minutes to develop, and recovers when the agonist is removed.



TRANSLOCATION OF RECEPTORS

Prolonged exposure to agonists often results in a gradual decrease in the number of receptors expressed on the cell surface, as a result of *internalisation* of the receptors. This is shown for β adrenoceptors and is a slower process than the uncoupling described above. Similar changes have been described for other types of receptor, including those for various peptides. The internalized receptors are taken into the cell by endocytosis of patches of the membrane, a process that normally depends on receptor phosphorylation and the subsequent binding of *arrestin* proteins to the phosphorylated receptor. This type of adaptation is common for hormone receptors and has obvious relevance to the effects produced when drugs are given for extended periods. It is generally an unwanted complication when drugs are used clinically.

EXHAUSTION OF MEDIATORS

In some cases, desensitisation is associated with depletion of an essential intermediate substance. Drugs such as **amphetamine**, which acts by releasing amines from nerve terminals, show marked tachyphylaxis because the amine stores become depleted.

ALTERED DRUG METABOLISM

Tolerance to some drugs, for example **barbiturates** and **ethanol**, occurs partly because repeated administration of the same dose produces a progressively lower plasma concentration, because of increased metabolic degradation. The degree of tolerance that results is generally modest, and in both of these examples other mechanisms contribute to the substantial tolerance that actually occurs.

PHYSIOLOGICAL ADAPTATION

Diminution of a drug's effect may occur because it is nullified by a homeostatic response. For example, the blood pressure-lowering effect of **thiazide diuretics** is limited because of a gradual activation of the renin–angiotensin system. Such homeostatic mechanisms are very common, and if they occur slowly the result will be a gradually developing tolerance. It is a common experience that many side effects of drugs, such as nausea or sleepiness, tend to subside even though drug administration is continued. We may assume that some kind of physiological adaptation is occurring, presumably associated with altered gene expression resulting in changes in the levels of various regulatory molecules, but little is known about the mechanisms involved.

Pharmacology

Lecture 7

Adrenergic Agonists

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Adrenergic drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block the activation of adrenergic receptors are termed sympatholytics. Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists).

Catecholamines are compounds containing a catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side chain. Pharmacologically, the most important ones are:

- **Noradrenaline** (**norepinephrine**), a transmitter released by sympathetic nerve terminals
- **Adrenaline** (**epinephrine**), a hormone secreted by the adrenal medulla.
- **Dopamine**, the metabolic precursor of noradrenaline and adrenaline, also a transmitter/neuromodulator in the central nervous system.
- **Isoprenaline** (**isoproterenol**), a synthetic derivative of noradrenaline, not present in the body.

Adrenergic Neuron:

Adrenergic neurons release norepinephrine as the primary neurotransmitter.

These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ.

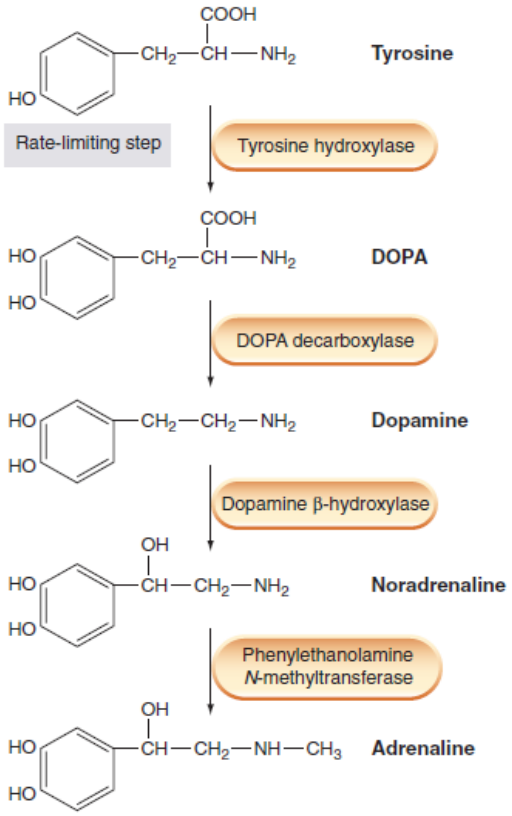


Figure 1: *Structures of the major catecholamines*

A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons, except that norepinephrine is the neurotransmitter instead of acetylcholine.

Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 2).

1. **Synthesis of norepinephrine:** Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme aromatic I-amino acid decarboxylase to form dopamine in the presynaptic neuron (figure 1).

2. **Storage of norepinephrine in vesicles:** Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by *reserpine*. Dopamine is next hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase.
3. **Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse. Drugs such as *guanethidine* block this release.

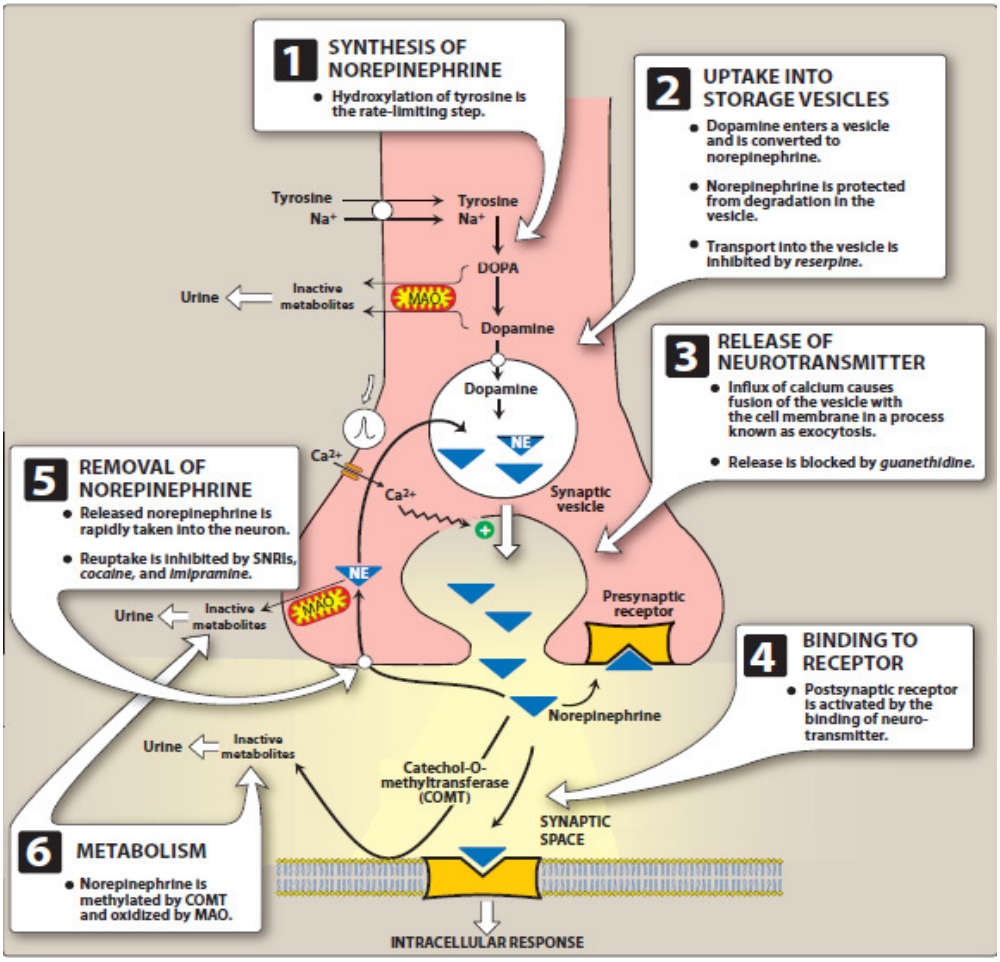


Figure 2: *Synthesis and release of norepinephrine from the adrenergic neuron. MAO = monoamine oxidase, SNRI = serotonin norepinephrine reuptake inhibitor.*

4. **Binding to receptors:** Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly α_2 subtype) that modulate the release of the neurotransmitter.
5. **Removal of norepinephrine:** Norepinephrine may

   1) Diffuse out of the synaptic space and enter the systemic circulation.

   2) Be metabolized to inactive metabolites by catechol-*O*-methyltransferase (COMT) in the synaptic space.

   3) Undergo reuptake back into the neuron. The reuptake by the neuronal membrane involves a sodium-chloride (Na^+/Cl^-)-dependent norepinephrine transporter (NET) that can be inhibited by tricyclic antidepressants (TCAs), such as *imipramine*, by serotonin–norepinephrine reuptake inhibitors such as *duloxetine*, or by *cocaine* (Figure 2).

   Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

6. **Potential fates of recaptured norepinephrine:** Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β, are classified on the basis of their responses to the adrenergic agonists *epinephrine*, *norepinephrine*, and *isoproterenol*.

Each of these main receptor types has a number of specific receptor subtypes that have been identified. Alterations in the primary structure of the receptors influence their affinity for various agents.

1. α-Adrenoceptors: The α-adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and *norepinephrine* (Figure 3). For α receptors, the rank order of potency and affinity is *epinephrine* ≥ *norepinephrine* >> *isoproterenol*. The α-adrenoceptors are subdivided into two subgroups, α_1 and α_2, based on their affinities for α agonists and blocking drugs. For example, the α_1 receptors have a higher affinity for *phenylephrine* than α_2 receptors. Conversely, the drug *clonidine* selectively binds to α_2 receptors and has less effect on α_1 receptors.

a. α1 Receptors: These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α_1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 3).

Receptor	Agonist	Antagonist	G Protein	Effects
α_1 type	Phenylephrine	Prazosin	G_q	↑ IP3, DAG common to all
α_{1A}		Tamsulosin		
α_{1B}				
α_{1D}				
α_2 type	Clonidine	Yohimbine	G_i	↓ cAMP common to all
α_{2A}	Oxymetazoline			
α_{2B}		Prazosin		
α_{2C}		Prazosin		
β type	Isoproterenol	Propranolol	G_s	↑ cAMP common to all
β_1	Dobutamine	Betaxolol		
β_2	Albuterol	Butoxamine		
β_3	Mirabegron			

b. α_2 Receptors: These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine. When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α_2 receptors on the presynaptic membrane (Figure 2). Stimulation of α_2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. [Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic

neuron, these receptors are acting as inhibitory autoreceptors.] α_2 receptors are also found on presynaptic parasympathetic neurons.

In contrast to α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.

c. Further subdivisions: The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example, *tamsulosin* is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets α_{1A} subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α_{1B} subtype found in the blood vessels.

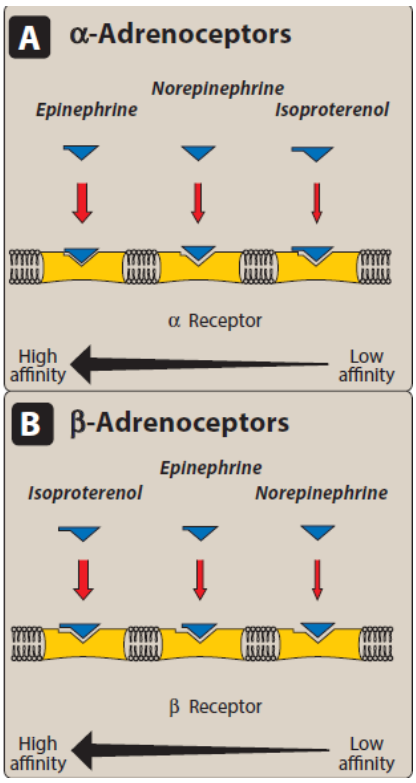
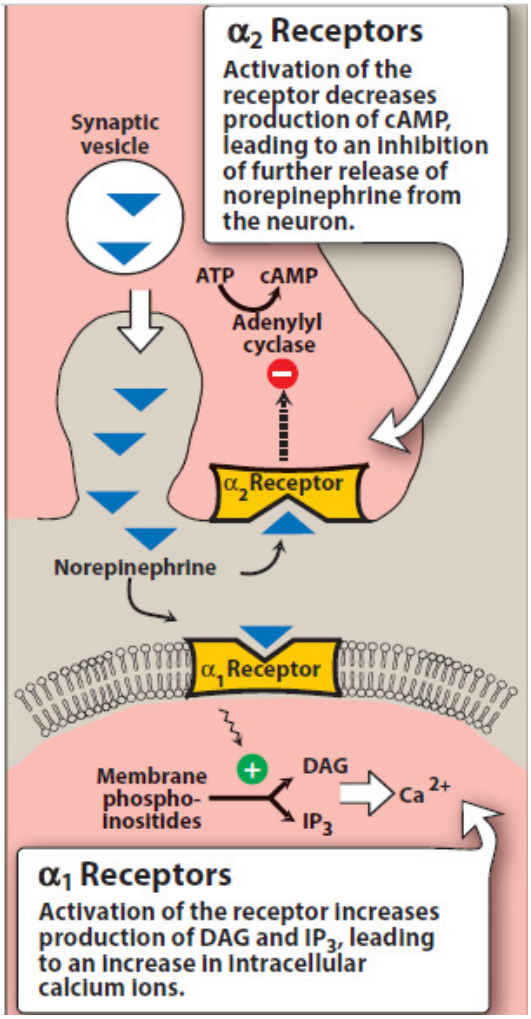


Figure 3: Types of adrenergic receptors

2. β-Adrenoceptors: Responses of β receptors differ from those of α receptors and are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and *norepinephrine* (Figure 3). For β receptors, the rank order of potency is *isoproterenol* > *epinephrine* > *norepinephrine*. The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists.

β_1 receptors have approximately equal affinities for *epinephrine* and *norepinephrine*, whereas β_2 receptors have a higher affinity for *epinephrine* than for *norepinephrine*. Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla. β_3 receptors are involved in lipolysis and also have effects on the detrusor muscle of the bladder. Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.



3. Distribution of receptors: Adrenergically innervated organs and tissues usually have a predominant type of receptor. For example, tissues such as the vasculature of skeletal muscle have both α_1 and β_2 receptors, but the β_2 receptors predominate. Other tissues may have one type of receptor almost exclusively. For example, the heart contains predominantly β_1 receptors.

4. Desensitization of receptors: Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable

for interaction with the ligand; 2) down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

Tissues and effects	α_1	α_2	β_1	β_2	β_3
SMOOTH MUSCLE					
Blood vessels	Constrict	Constrict/dilate	–	Dilate	–
Bronchi	Constrict	–	–	Dilate	–
Gastrointestinal tract	Relax	Relax (presynaptic effect)	–	Relax	–
Gastrointestinal sphincters	Contract	–	–	–	–
Uterus	Contract	–	–	Relax	–
Bladder detrusor	–	–	–	Relax	Relax
Bladder sphincter	Contract	–	–	–	–
Seminal tract	Contract	–	–	Relax	–
Iris (radial muscle)	Contract	–	–	–	–
Ciliary muscle	–	–	–	Relax	–
HEART					
Rate	–	–	Increase	Increase[a]	–
Force of contraction	–	–	Increase	Increase[a]	–
OTHER TISSUES/CELLS					
Skeletal muscle	–	–	–	Tremor Increased muscle mass and speed of contraction Glycogenolysis	Thermogenesis
Liver (hepatocytes)	Glycogenolysis	–	–	Glycogenolysis	–
Fat (adipocytes)	–	–	–	–	Lipolysis Thermogenesis
Pancreatic islets (B cells)	–	Decrease insulin secretion	–	–	–
Salivary gland	K^+ release	–	Amylase secretion	–	–
Platelets	–	Aggregation	–	–	–
Mast cells	–	–	–	Inhibition of histamine release	–
Brain stem	–	Inhibits sympathetic outflow	–	–	–
NERVE TERMINALS					
Adrenergic	–	Decrease release	–	Increase release	–
Cholinergic	–	Decrease release	–	–	–

	α_1	α_2	β_1	β_2	β_3
Second messengers and effectors	Phospholipase C activation ↑ Inositol trisphosphate ↑ Diacylglycerol ↑ Ca^{2+}	↓ cAMP ↓ Calcium channels ↑ Potassium channels	↑ cAMP	↑ cAMP	↑ cAMP
Agonist potency order	NA > A >> ISO	A > NA >> ISO	ISO > NA > A	ISO > A > NA	ISO > NA = A
Selective agonists	Phenylephrine Methoxamine	Clonidine	Dobutamine Xamoterol	Salbutamol Terbutaline Salmeterol Formoterol Clenbuterol	Mirabegron
Selective antagonists	Prazosin Doxazocin	Yohimbine Idazoxan	Atenolol Metoprolol	Butoxamine	–

A, adrenaline; ISO, isoprenaline; NA, noradrenaline.

Pharmacology

Lecture 8

Adrenergic Agonists

Characteristics of Adrenergic Agonist:

Most of the adrenergic drugs are derivatives of β-phenylethylamine (Figure 1). Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are 1) the number and location of OH substitutions on the benzene ring and 2) the nature of the substituent on the amino nitrogen.

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as *epinephrine*, *norepinephrine*, *isoproterenol*, and *dopamine*) are called catecholamines. These compounds share the following properties:

1. High potency: Catecholamines (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors.

2. Rapid inactivation: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, as well as by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.

3. Poor penetration into the CNS: Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

B. Non-catecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include *phenylephrine*, *ephedrine*, and

amphetamine (Figure 1). These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. Increased lipid solubility of many of the non-catecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Mechanism of action of adrenergic agonists:

1. Direct-acting agonists: These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla (Figure 2). Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, and *phenylephrine*.

2. Indirect-acting agonists: These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (Figure 2).

The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include *cocaine* and *amphetamines*, respectively.

3. Mixed-action agonists: *Ephedrine* and its stereoisomer, *pseudoephedrine*, both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron (Figure 2).

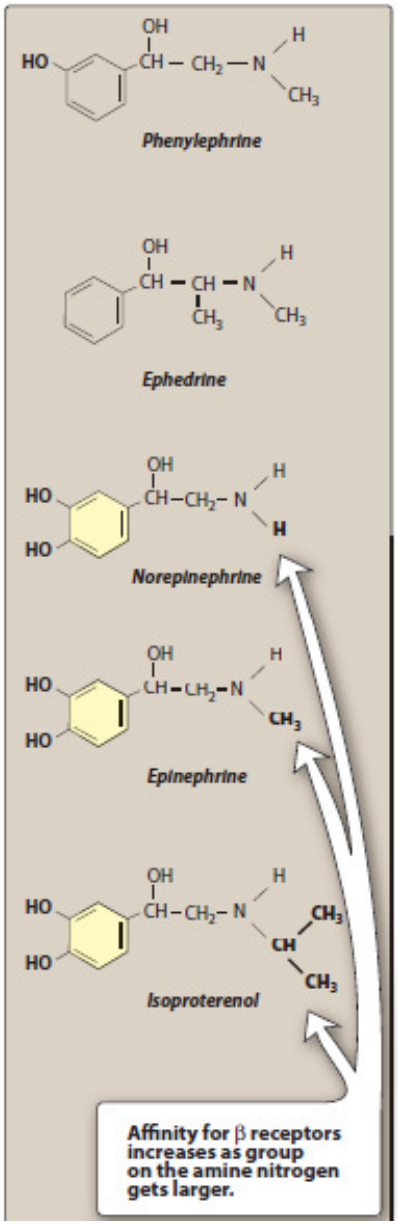


Figure 1: *Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.*

Direct-acting agonists:

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

A. Epinephrine

Epinephrine is one of the four catecholamines (*epinephrine*, *norepinephrine*, *dopamine*, and *dobutamine*) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal medulla, *norepinephrine* is methylated to yield *epinephrine*, which is stored in chromaffin cells along with *norepinephrine*. On stimulation, the adrenal medulla releases about 80% *epinephrine* and 20% *norepinephrine* directly into the circulation.

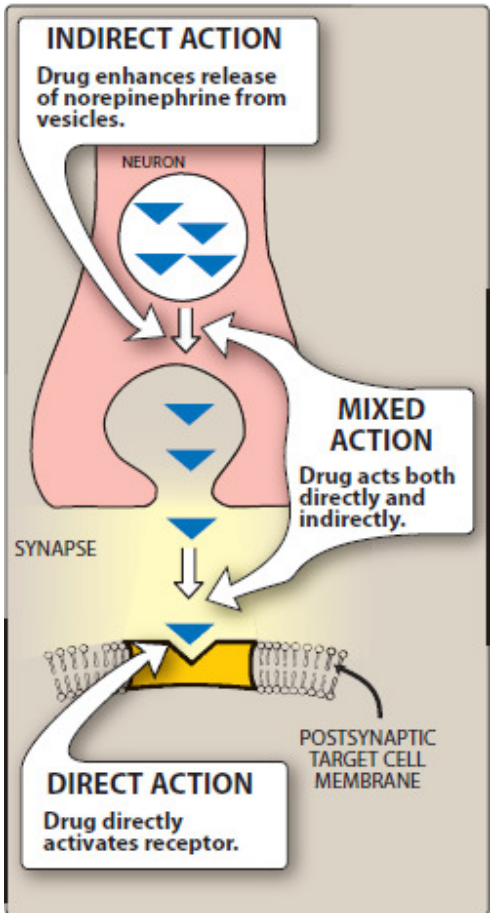


Figure 2: Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

1. Actions:

a. Cardiovascular: The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotrope: β1 action) and increases its rate of contraction (positive chronotrope: β1 action). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. *Epinephrine* activates β1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor.

Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β2 effects). Renal blood flow

is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β2 receptor–mediated vasodilation in the skeletal muscle vascular bed (Figure 3).

b. Respiratory: *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). It also inhibits the release of allergy mediators such as histamines from mast cells.

c. Hyperglycemia: *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect).

d. Lipolysis: *Epinephrine* initiates lipolysis through agonist activity on the β receptors of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

2. Therapeutic uses:

a. Bronchospasm: *Epinephrine* is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function.

Thus, in treatment of acute asthma and anaphylactic shock, *epinephrine* is the drug of choice and can be life saving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves. However, selective β2 agonists, such as *albuterol*, are favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effects.

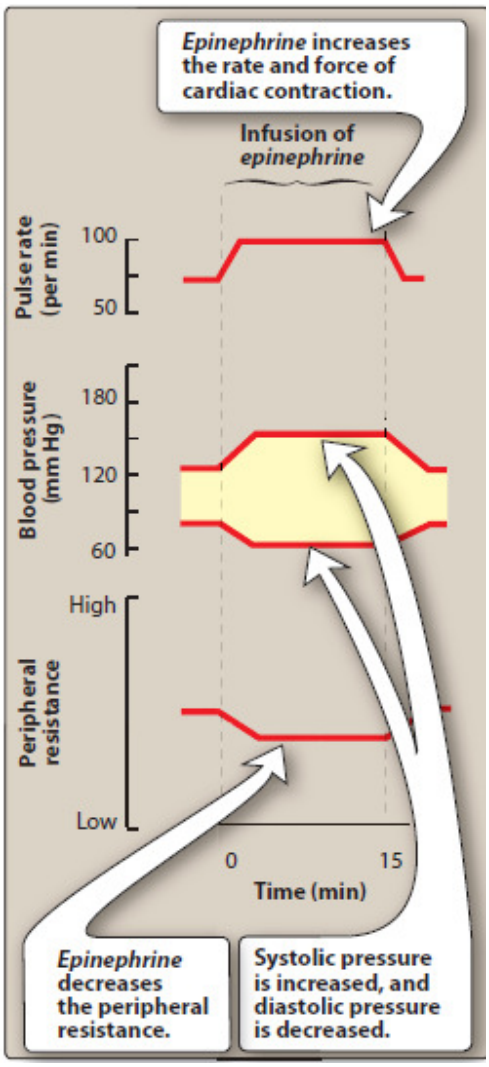


Figure 3: Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

b. Anaphylactic shock: *Epinephrine* is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens.

c. Cardiac arrest: *Epinephrine* may be used to restore cardiac rhythm in patients with cardiac arrest.

d. Anesthetics: Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of *epinephrine*. *Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. This allows the local anesthetic to persist at the injection site before being absorbed into the systemic circulation.

B. Norepinephrine

Because *norepinephrine* is the neurotransmitter of adrenergic nerves, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the α-adrenergic receptor is most affected.

1. Cardiovascular actions:

a. Vasoconstriction: *Norepinephrine* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α1 effect). Both systolic and diastolic blood pressures increase (Figure 4). [Note: *Norepinephrine* causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via β2 receptors on blood vessels supplying skeletal muscles. The weak β2 activity of *norepinephrine* also explains why it is not useful in the treatment of asthma or anaphylaxis.]

b. Baroreceptor reflex: *Norepinephrine* increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which is sufficient to counteract the local actions of *norepinephrine* on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug (Figure 4). When *atropine*, which blocks the transmission of vagal

effects, is given before *norepinephrine*, stimulation of the heart by *norepinephrine* is evident as tachycardia.

2. Therapeutic uses: *Norepinephrine* is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

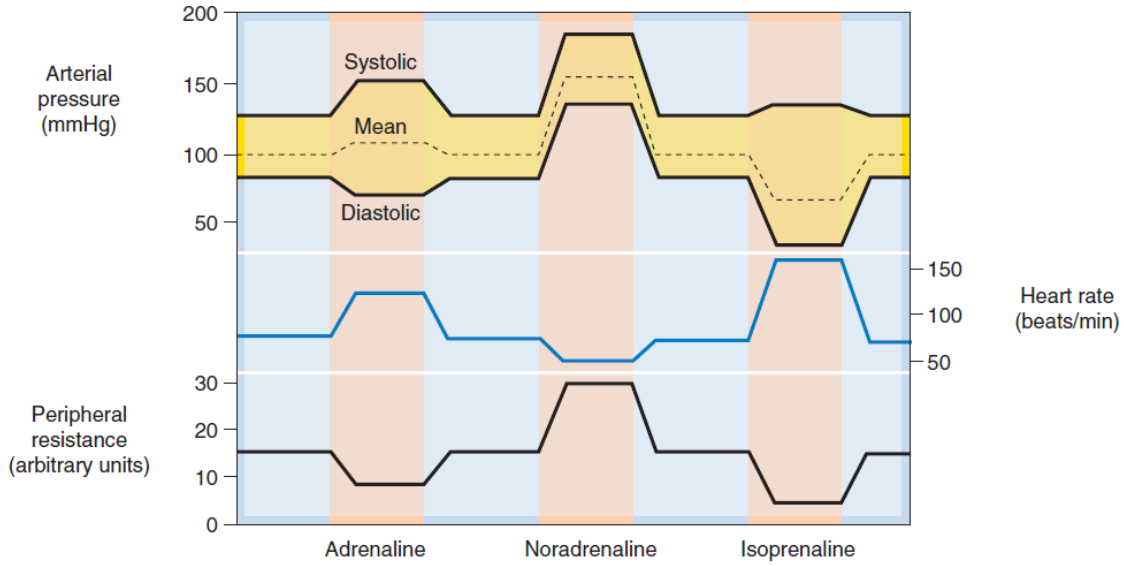


Figure 4: *Schematic representation of the cardiovascular effects of intravenous infusions of adrenaline, noradrenaline and isoprenaline in humans. Noradrenaline (predominantly α agonist) causes vasoconstriction and increased systolic and diastolic pressure, with a reflex bradycardia. Isoprenaline (β agonist) is a vasodilator, but strongly increases cardiac force and rate. Mean arterial pressure falls. Adrenaline combines both actions.*

C. Isoproterenol

Isoproterenol is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its non-selectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant.

Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output (Figure 4). It is as active as *epinephrine* in this action. *Isoproterenol* also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressures (Figure 4). *Isoproterenol* is a potent bronchodilator (β2 effect). The use of *isoproterenol* has largely been replaced with other drugs, but it may be useful in

atrioventricular (AV) block. The adverse effects of *isoproterenol* are similar to those of *epinephrine*.

D. Dopamine

Dopamine [DOE-pa-meen], the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate α- and β-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors.

In addition, D1 and D2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

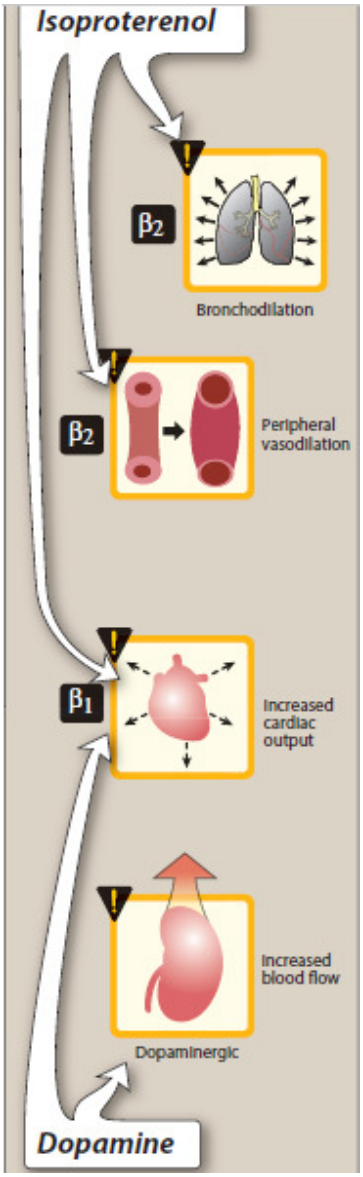


Figure 5: Clinically important actions of *isoproterenol* and *dopamine*.

1. Actions:

a. Cardiovascular: *Dopamine* exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects (Figure 6.13). At very high doses, *dopamine* activates α1 receptors on the vasculature, resulting in vasoconstriction.

b. Renal and visceral: *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera (Figure 6.13).

These receptors are not affected by α- or β-blocking drugs. Therefore, *dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

2. Therapeutic uses: *Dopamine* is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above.

E. Fenoldopam

Fenoldopam is an agonist of peripheral dopamine D1 receptors. It is used as rapid-acting vasodilators to treat sever hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. *Fenoldopam* is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed with this agent.

F. Dobutamine

Dobutamine is a synthetic, direct-acting catecholamine that is a β_1 receptor agonist. It increases cardiac rate and output with few vascular effects. *Dobutamine* is used to increase cardiac output in acute heart failure, as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs.

G. Oxymetazoline

Oxymetazoline is a direct-acting synthetic adrenergic agonist that stimulates both α1- and α2-adrenergic receptors. *Oxymetazoline* is found in many over-the-counter short-term nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. *Oxymetazoline* directly stimulates α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion. It is absorbed in the

systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping.

Local irritation and sneezing may occur with intranasal administration. Rebound congestion and dependence are observed with long-term use.

H. Phenylephrine

Phenylephrine is a direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally. The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate).

Large doses can cause hypertensive headache and cardiac irregularities. *Phenylephrine* acts as a nasal decongestant when applied topically or taken orally. *Phenylephrine* is also used in ophthalmic solutions for mydriasis.

I. Clonidine

Clonidine is an **α2 agonist** that is used for the treatment of hypertension. It can also be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines. *Clonidine* acts centrally on presynaptic α2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of *clonidine* are lethargy, sedation, constipation, and xerostomia.

Abrupt discontinuance must be avoided to prevent rebound hypertension.

J. Albuterol and terbutaline

Albuterol and *terbutaline* are short-acting β_2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler. *Albuterol* is the short-acting β_2 agonist of choice for the management of acute asthma symptoms.

Terbutaline is also used off-label as a uterine relaxant to suppress premature labor. One of the most common side effects of these agents is tremor, but patients tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety.

When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β1 receptor activation), especially in patients with underlying cardiac disease. Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided.

K. Salmeterol and formoterol

Salmeterol and *formoterol* are long acting β agonists (LABAs) that are β_2 selective. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol*. Unlike *formoterol*, however, *salmeterol* has a somewhat delayed onset of action. These agents are not recommended as monotherapy, but are highly efficacious when combined with a corticosteroid. *Salmeterol* and *formoterol* are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.

L. Mirabegron

Mirabegron is a β_3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder. *Mirabegron* may increase blood pressure and should not be used in patients with uncontrolled hypertension.

Pharmacology

Lecture 9

INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of *amphetamine* is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α1 agonist action on the vasculature, as well as β1-stimulatory effects on the heart.

Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. Thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and therapeutic uses of *amphetamine* and its derivatives are discussed under stimulants of the CNS.

B. Tyramine

Tyramine is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism.

Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor episodes. Like *amphetamines*, *tyramine* can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

C. Cocaine

Cocaine is unique among local anesthetics in having the ability to block the sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in

the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocaine*. In addition, the duration of action of epinephrine and norepinephrine is increased. Like *amphetamines*, it can increase blood pressure by α1 agonist actions and β stimulatory effects.

MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine and *pseudoephedrine* are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent.

Ephedrine and *pseudoephedrine* are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption orally and penetrate into the CNS, but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension. *Ephedrine* produces bronchodilation, but it is less potent and slower acting than *epinephrine* or *isoproterenol*. It was previously used to prevent asthma attacks but has been replaced by more effective medications. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of *ephedrine* is declining because of the availability of better, more potent agents that cause fewer adverse effects. *Ephedrine*-containing herbal supplements (mainly ephedra-containing products) have been banned by the U.S. Food and Drug Administration because of life-threatening cardiovascular reactions.] *Pseudoephedrine* is primarily used orally to treat nasal and sinus congestion. *Pseudoephedrine* has been illegally used to produce *methamphetamine*.

Adrenergic Antagonists

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system.

α-ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. [Note: β receptors, including β1 adrenoceptors on the heart, are not affected by α blockade.]. The α-adrenergic blocking agents, *phenoxybenzamine* and *phentolamine*, have limited clinical applications.

A. Phenoxybenzamine

Phenoxybenzamine is nonselective, linking covalently to both α1 and α2 receptors. The block is irreversible and noncompetitive, and the only way the body can overcome the block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of *phenoxybenzamine* last about 24 hours. After the drug is injected, a delay of a few hours occurs before a blockade develops.

Actions:

a. Cardiovascular effects: By blocking α receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic inhibitory α2 receptors in the heart can contribute to an increased cardiac output. [Note: Blocking these receptors results in more norepinephrine release, which stimulates β1 receptors on the heart, increasing cardiac output.] Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

b. Epinephrine reversal: All α-adrenergic blockers reverse the α agonist actions of *epinephrine*. For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of β2 receptors is not blocked. Therefore, in the presence of *phenoxybenzamine*, the systemic blood pressure decreases in response to *epinephrine* (Figure 1). [Note: The actions of *norepinephrine* are not reversed but are diminished because *norepinephrine* lacks significant β agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure β agonist (Figure 1).

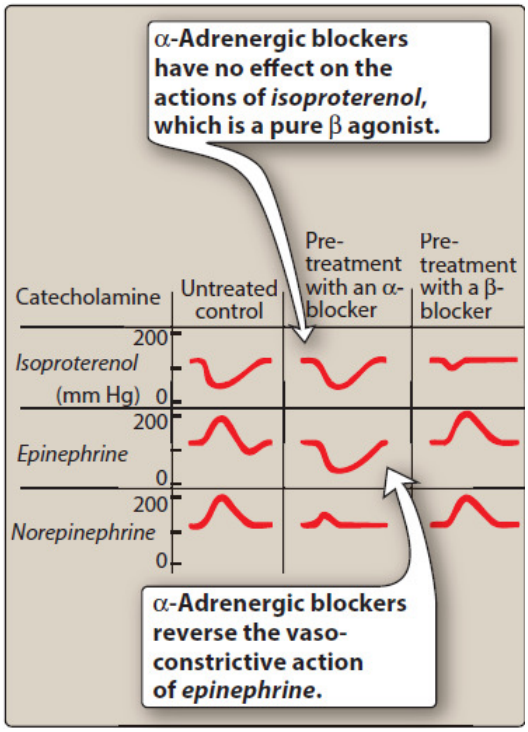


Figure 1: Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and *norepinephrine*.

2. Therapeutic uses: *Phenoxybenzamine* is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. It may be used prior to surgical removal of the tumor to prevent a hypertensive crisis.

3. Adverse effects: *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex. *Phenoxybenzamine* should be used with caution in patients with cerebrovascular or cardiovascular disease.

B. Phentolamine

In contrast to *phenoxybenzamine*, *phentolamine* produces a competitive block of α1 and α2 receptors that lasts for approximately 4 hours after a single injection. Like *phenoxybenzamine*, it produces postural hypotension and causes *epinephrine* reversal. *Phentolamine*-induced reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex and by blocking the α2 receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain, and *phentolamine* is contraindicated in patients with coronary artery disease.

C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

Prazosin, *terazosin*, and *doxazosin* are selective competitive blockers of the α1 receptor. In contrast to *phenoxybenzamine* and *phentolamine*, they are useful in the treatment of hypertension. *Tamsulosin* and *alfuzosin* are examples of other selective α1 antagonists indicated for the treatment of benign prostatic hyperplasia (BPH). Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

1. Mechanism of action: All of these agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Tamsulosin has the least effect on blood pressure because it is less selective for α1B receptors found in the blood vessels and more selective for α1A receptors in the prostate and bladder. Blockade of the α1A receptors a decrease tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

2. Therapeutic uses: Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response that can result in syncope (fainting).

This action, termed a "first-dose" effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared to other antihypertensives, α1 antagonists are not used as monotherapy for the treatment of hypertension. The α1 receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH.

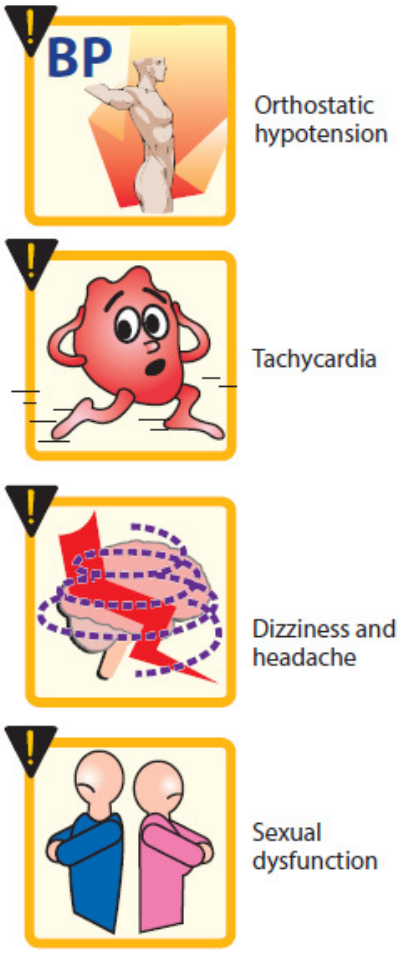


Figure 2: Some adverse effects commonly observed with nonselective α-adrenergic blocking agents.

D. Yohimbine

Yohimbine is a selective competitive α2-blocker. It is found as a component of the bark of the yohimbe tree and has been used as a sexual stimulant and in the treatment of erectile dysfunction.

Its use in the treatment of these disorders is not recommended, due to lack of demonstrated efficacy. *Yohimbine* works at the level of the CNS to increase sympathetic outflow to the periphery. It is contraindicated in cardiovascular disease, psychiatric conditions, and renal dysfunction because it may worsen these conditions.

III. β-ADRENERGIC BLOCKING AGENTS

All of the clinically available β-blockers are competitive antagonists.

Nonselective β-blockers act at both β1 and β2 receptors, whereas cardioselective β antagonists primarily block β1 receptors. [Note: There are no clinically useful β2 antagonists.] These drugs also differ in intrinsic sympathomimetics activity, CNS effects, blockade of sympathetic

Although all β-blockers lower blood pressure, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. B Blockers are effective in treating hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in "-olol" except for *labetalol* and *carvedilol*.]

A. Propranolol: A nonselective β antagonist

Propranolol is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors with equal affinity. Sustainedrelease preparations for once-a-day dosing are available.

1. Actions:

a. Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 3). It directly depresses sinoatrial and atrioventricular nodal activity.

The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina. The β-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).

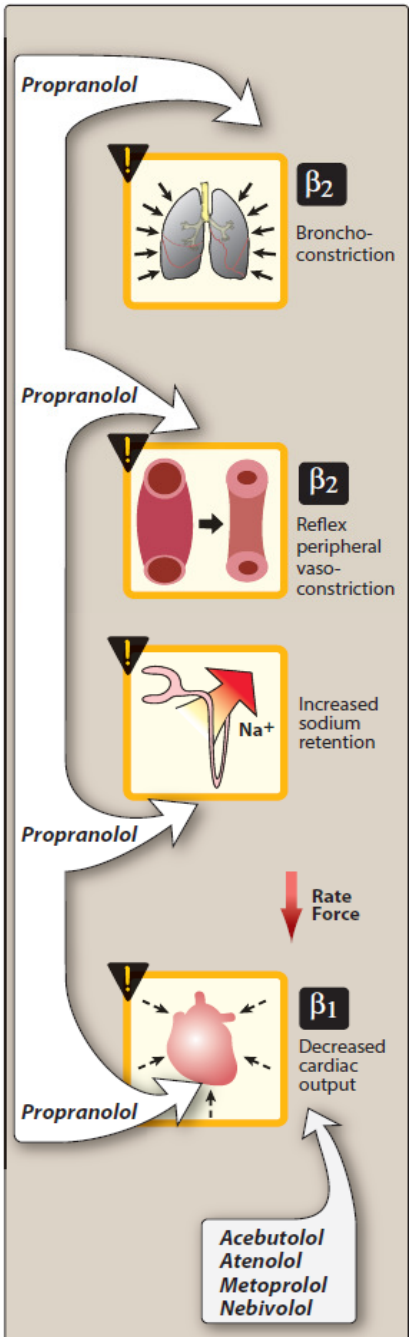


Figure 3: Actions of *propranolol* and otherβ-blockers.

b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance (Figure 3). The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of *propranolol*. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

c. Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (Figure 3). This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β-blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

d. Disturbances in glucose metabolism: β blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if *propranolol* is given to a diabetic patient receiving *insulin*, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after *insulin* injection. β-blockers also attenuate the normal physiologic response to hypoglycemia.

e. Blocked action of isoproterenol: Nonselective β-blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* (β1, β2 agonist) on the cardiovascular system. Thus, in the presence of a β-blocker, *isoproterenol* does not produce cardiac stimulation (β1 mediated) or reductions in mean arterial pressure and diastolic pressure (β2 mediated).
[Note: In the presence of a nonselective β-blocker, *epinephrine* no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by α receptors) remains unimpaired. The actions of *norepinephrine* on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.]

2. Therapeutic uses:

a. Hypertension: *Propranolol* does not reduce blood pressure in people with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the antihypertensive effects.

b. Angina pectoris: *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. *Propranolol* is, thus, useful in the chronic management of stable angina.

c. Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery.
The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

d. Migraine: *Propranolol* is effective in reducing migraine episodes when used prophylactically. It is one of the more useful β-blockers for this indication, due to its lipophilic nature that allows it to penetrate the CNS. [Note: For the acute management of migraine, serotonin agonists such as *sumatriptan* are used, as well as other drugs.]

e. Hyperthyroidism: *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

3. Pharmacokinetics: After oral administration, *propranolol* is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation.
The volume of distribution of *propranolol* is quite large (4 L/kg), and the drug readily crosses the blood–brain barrier due to its high lipophilicity.
Propranolol is extensively metabolized, and most metabolites are excreted in the urine.

4. Adverse effects:
a. Bronchoconstriction: *Propranolol* has the potential to cause significant bronchoconstriction due to blockade of β2 receptors (Figure 4). Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, *propranolol* is contraindicated in patients with COPD or asthma.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

c. Sexual impairment: Because ejaculation in the male is mediated through α-adrenergic activation, β-blockers do not affect ejaculation or internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β receptor blockade.

d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β-blockers can prevent the counter regulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers.

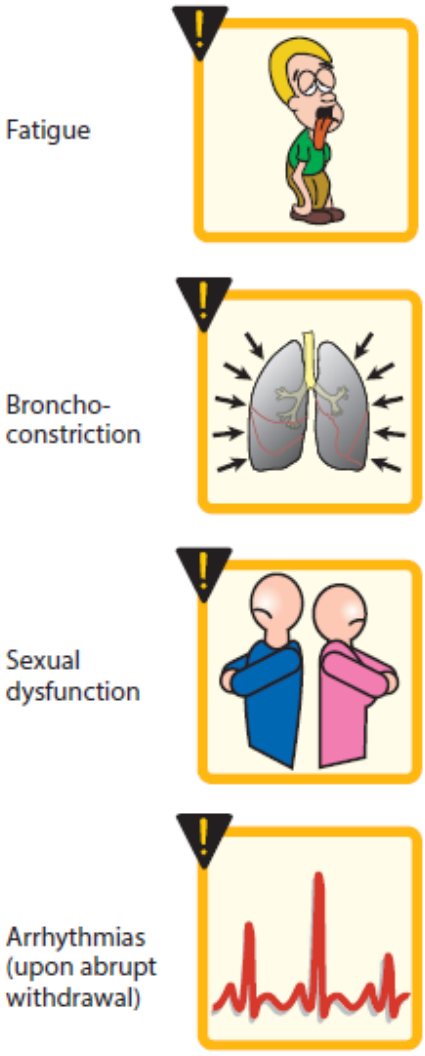


Figure 4: Adverse effects commonly observed in individuals treated with *propranolol.*

A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated mainly by β2 and β3 receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β-blockers have increased low density lipoprotein ("bad" cholesterol), increased triglycerides, and reduced high-density lipoprotein ("good" cholesterol). These effects on the serum lipid profile may be less pronounced with the use of β1-selective antagonists such as *metoprolol*.

e. CNS effects: *Propranolol* has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects

may be seen with more hydrophilic β-blockers (for example, *atenolol*), since they do not cross the blood–brain barrier as readily.

B. Nadolol and timolol: Nonselective β antagonists

Nadolol and *timolol* also block β1- and β2-adrenoceptors and are more potent than *propranolol*. *Nadolol* has a very long duration of action. *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma and, occasionally, for systemic treatment of hypertension.

1. Treatment of glaucoma: β-blockers, such as topically applied *timolol*, *betaxolol*, or *carteolol*, are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size. When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24 hours.

The β-blockers are only used for chronic management of glaucoma. In an acute attack of glaucoma, *pilocarpine* is still the drug of choice for emergency lowering of intraocular pressure.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide*, and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: Selective β1 antagonists

Drugs that preferentially block the β1 receptors minimize the unwanted bronchoconstriction (β2 effect) seen with *propranolol* use in asthma patients. Cardioselective β-blockers, such as *acebutolol*, *atenolol*, and *metoprolol*, antagonize β1 receptors at doses 50- to 100-fold less than

those required to block β2 receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Since β1 selectivity of these agents is lost at high doses, they may antagonize β2 receptors.]

1. Actions: These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (Figure 3). *Esmolol* has a very short half-life due to metabolism of an ester linkage. It is only available intravenously and is used to control blood pressure or heart rhythm during surgery or diagnostic procedures. In contrast to *propranolol*, the cardioselective β-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism.
Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised. In addition to its cardioselective β blockade, *nebivolol* releases nitric oxide from endothelial cells and causes vasodilation.

2. Therapeutic uses: The cardioselective β-blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina.
Bisoprolol and the extended-release formulation of *metoprolol* are indicated for the management of chronic heart failure. Because these drugs have less effect on peripheral vascular β2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. Actions:

a. Cardiovascular: *Acebutolol* (β1-selective antagonist) and *pindolol* (nonselective β-blocker) are not pure antagonists. These drugs also have the ability to weakly stimulate both β1 and β2 receptors (Figure 5) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a diminished effect on cardiac rate and cardiac output compared to that of β-blockers without ISA.

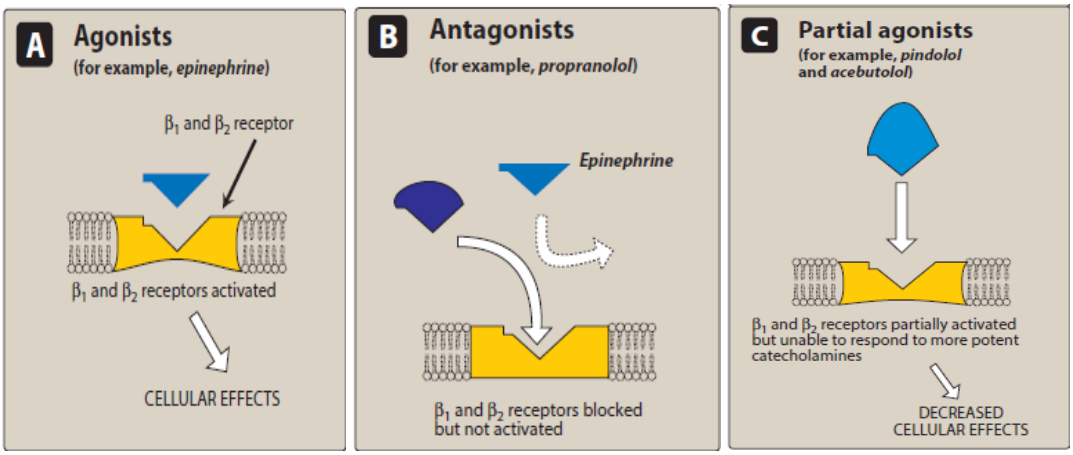


Figure 5: Comparison of agonists, antagonists, and partial agonists of β adrenoceptors.

b. Decreased metabolic effects: β-blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

2. Therapeutic use in hypertension: β-blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. [Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.].

E. Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

1. Actions: *Labetalol* and *carvedilol* are nonselective β-blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure.

They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

2. Therapeutic use in hypertension and heart failure: *Labetalol* is employed as an alternative to *methyldopa* in the treatment of pregnancy- induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure. β-blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, *carvedilol* as well as *metoprolol* and *bisoprolol* are beneficial in patients

with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time.

3. Adverse effects: Orthostatic hypotension and dizziness are associated with α1 blockade. Below Figure summarizes the receptor specificities and uses of the β-adrenergic antagonists.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

Pharmacology Lecture 10

Drugs Affecting neurotransmitter release or uptake

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron or by other ways. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically.

Drugs that affect noradrenaline synthesis:

Only a few clinically important drugs affect noradrenaline synthesis directly. Examples are **α-methyltyrosine**, which inhibits tyrosine hydroxylase, and **carbidopa**, a hydrazine derivative of dopa, which inhibits dopa decarboxylase and is used in the treatment of parkinsonism .

Methyldopa, still used in the treatment of hypertension during pregnancy, is taken up by noradrenergic neurons, where it is converted to the false transmitter α-methylnoradrenaline. This substance is not deaminated within the neuron by MAO, so it accumulates and displaces noradrenaline from the synaptic vesicles. α-Methylnoradrenaline is released in the same way as noradrenaline, but is less active than noradrenaline on α1 receptors and thus is less effective in causing vasoconstriction. On the other hand, it is more active on presynaptic (α2) receptors, so the autoinhibitory feedback mechanism operates more strongly than normal, thus reducing transmitter release below the normal levels. Both of these effects (as well as a central effect, probably caused by the same cellular mechanism) contribute to the hypotensive action. It produces side effects typical of centrally acting antiadrenergic drugs (e.g. sedation), as well as carrying a risk of immune haemolytic reactions and liver toxicity, so it is now little used, except for hypertension in late pregnancy where there is considerable experience of its use and no suggestion of harm to the unborn baby.

Drugs that affect noradrenaline storage:

Reserpine is an alkaloid from the shrub *Rauwolfia*, which has been used in India for centuries for the treatment of mental disorders. Reserpine, at very low concentration, blocks the transport of noradrenaline and other amines into synaptic vesicles, by blocking the vesicular monoamine transporter. Noradrenaline accumulates instead in the cytoplasm, where it is degraded by MAO. The noradrenaline content of tissues drops to a low level, and sympathetic transmission is blocked. Reserpine also causes depletion of 5-HT and dopamine from neurons in the brain, in which these amines are transmitters. Reserpine is now used only experimentally, but was at one time used as an antihypertensive drug. Its central effects, especially depression, which probably result from impairment of noradrenergic and 5-HT-mediated transmission in the brain, were a serious problem.

Drugs that affect noradrenaline release:

Drugs can affect noradrenaline release in four main ways:

- by directly blocking release (noradrenergic neuron-blocking drugs)
- by evoking noradrenaline release in the absence of nerve terminal depolarisation (indirectly acting sympathomimetic drugs)
- by acting on presynaptic receptors that indirectly inhibit or enhance depolarisation-evoked release; examples include α2 agonists, angiotensin II, dopamine and prostaglandins.
- by increasing or decreasing available stores of noradrenaline

Noradrenergic neuron-blocking drugs:

Noradrenergic neuron-blocking drugs (e.g. **guanethidine**) were first discovered in the mid-1950s when alternatives to ganglion-blocking drugs, for use in the treatment of hypertension, were being sought. The main effect of guanethidine is to inhibit the release of noradrenaline from sympathetic nerve terminals. It has little effect on the adrenal medulla, and none on nerve terminals that release transmitters other than noradrenaline. Drugs very similar to it include **bretylium**, **bethanidine** and **debrisoquin.**

Actions

Drugs of this class reduce or abolish the response of tissues to sympathetic nerve stimulation, but do not affect (or may potentiate) the effects of circulating noradrenaline. The action of guanethidine on noradrenergic transmission is complex. It is selectively accumulated by noradrenergic nerve terminals, being a substrate for NET. Its initial blocking activity is due to block of impulse conduction in the nerve terminals that selectively accumulate the drug. Its action is prevented by drugs, such as *tricyclic antidepressants*, that block NET.

Guanethidine is also concentrated in synaptic vesicles by means of the vesicular transporter VMAT, possibly interfering with their ability to undergo exocytosis, and also displacing noradrenaline. In this way, it causes a gradual and long-lasting depletion of noradrenaline in sympathetic nerve endings, similar to the effect of reserpine.

Guanethidine, bethanidine and debrisoquin are no longer used clinically, now that better antihypertensive drugs are available. Although extremely effective in lowering blood pressure, they produce severe side effects associated with the loss of sympathetic reflexes. The most troublesome are postural hypotension, diarrhea, nasal congestion and failure of ejaculation.

Indirectly acting sympathomimetics amine:

The most important drugs in the indirectly acting sympathomimetic amine category are **tyramine**, **amphetamine** and **ephedrine**, which are structurally related to noradrenaline. Drugs that act similarly and are used for their central effects include **methylphenidate** and **atomoxetine**.

These drugs have only weak actions on adrenoceptors, but sufficiently resemble noradrenaline to be transported into nerve terminals by NET. Once inside the nerve terminals, they are taken up into the vesicles by VMAT, in exchange for noradrenaline, which escapes into the cytosol. Some of the cytosolic noradrenaline is degraded by MAO, while the rest escapes via NET, in exchange for the foreign monoamine, to act on postsynaptic receptors (Fig. 1). Exocytosis is not involved in the release process, so their actions do not require the presence of Ca2+. They are not completely specific in their actions, and act partly by a direct effect on adrenoceptors, partly by inhibiting NET

(thereby enhancing the effect of the released noradrenaline) and partly by inhibiting MAO.

Table 1: Drugs that affect noradrenaline synthesis, release or uptake

Drug	Main action	Uses/function	Unwanted effects	Pharmacokinetic aspects
Drugs affecting NA synthesis				
α-Methyl-p-tyrosine	Inhibits tyrosine hydroxylase	Occasionally used in phaeochromocytoma	Hypotension, sedation	–
Carbidopa	Inhibits dopa decarboxylase	Used as adjunct to levodopa to prevent peripheral effects	–	Absorbed orally Does not enter brain
Methyldopa	False transmitter precursor	Hypertension in pregnancy	Hypotension, drowsiness, diarrhoea, impotence, hypersensitivity reactions	Absorbed slowly by mouth Excreted unchanged or as conjugate Plasma $t_{1/2}$ ~6 h
L-dihydroxyphenylserine (L-DOPS)	Converted to NA by dopa decarboxylase, thus increasing NA synthesis and release	Orthostatic hypotension	Not known	Absorbed orally Duration of action ~6 h
Drugs that release NA (indirectly acting sympathomimetic amines)				
Tyramine	NA release	No clinical uses Present in various foods	As norepinephrine	Normally destroyed by MAO in gut Does not enter brain
Amphetamine	NA release, MAO inhibitor, NET inhibitor, CNS stimulant	Used as CNS stimulant in narcolepsy, also (paradoxically) in hyperactive children Appetite suppressant Drug of abuse	Hypertension, tachycardia, insomnia Acute psychosis with overdose Dependence	Well absorbed orally Penetrates freely into brain Excreted unchanged in urine Plasma $t_{1/2}$ ~12 h, depending on urine flow and pH
Ephedrine	NA release, β agonist, weak CNS stimulant action	Nasal decongestion	As amphetamine but less pronounced	Similar to amphetamine aspects

Drugs that inhibit NA release				
Reserpine	Depletes NA stores by inhibiting VMAT	Hypertension (obsolete)	As methyldopa Also depression, parkinsonism, gynaecomastia	Poorly absorbed orally Slowly metabolised Plasma $t_{1/2}$ ~100 h Excreted in milk
Guanethidine	Inhibits NA release Also causes NA depletion and can damage NA neurons irreversibly	Hypertension (obsolete)	As methyldopa Hypertension on first administration	Poorly absorbed orally Mainly excreted unchanged in urine Plasma $t_{1/2}$ ~100 h
Drugs affecting NA uptake				
Imipramine	Blocks neuronal transporter (NET) Also has atropine-like action	Depression	Atropine-like side effects Cardiac dysrhythmias in overdose	Well absorbed orally 95% bound to plasma protein Converted to active metabolite (desmethylimipramine) Plasma $t_{1/2}$ ~4 h
Cocaine	Local anaesthetic; blocks NET CNS stimulant	Rarely used local anaesthetic Major drug of abuse	Hypertension, excitement, convulsions, dependence	Well absorbed orally or intranasally

As would be expected, the effects of these drugs are strongly influenced by other drugs that modify noradrenergic transmission. Thus reserpine and 6-hydroxydopamine abolish their effects by depleting the terminals of noradrenaline. MAO inhibitors, on the other hand, strongly potentiate their effects by preventing inactivation, within the terminals, of the transmitter displaced from the vesicles. MAO inhibition particularly enhances the action of tyramine, because this substance is itself a substrate for MAO. Normally, dietary tyramine is destroyed by MAO in the gut wall and liver before reaching the systemic circulation. When MAO is inhibited this is prevented, and ingestion of tyramine-rich foods such as fermented cheese (e.g. ripe Brie) can then provoke a sudden and dangerous rise in blood pressure. Inhibitors of NET, such as **imipramine** (Table 1), interfere with the effects of indirectly acting sympathomimetic amines by preventing their uptake into the nerve terminals.

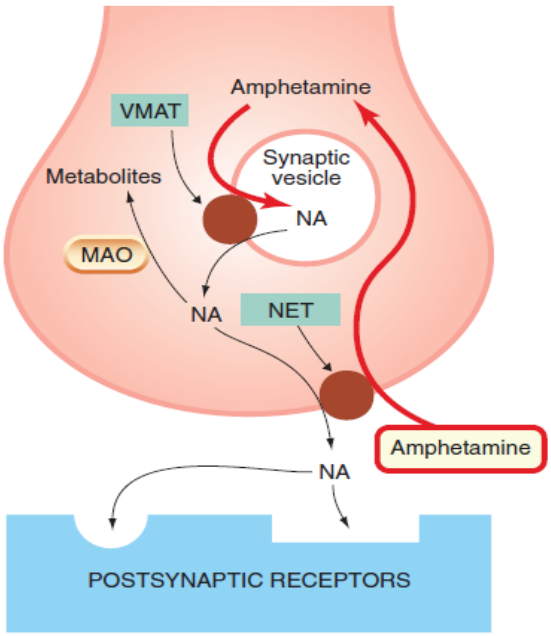


Figure 1: *The mode of action of amphetamine, an indirectly acting sympathomimetic amine. Amphetamine enters the nerve terminal via the noradrenaline transporter (NET) and enters synaptic vesicles via the vesicular monoamine transporter (VMAT), in exchange for NA, which accumulates in the cytosol. Some of the NA is degraded by monoamine oxidase (MAO) within the nerve terminal and some escapes, in exchange for amphetamine via the noradrenaline transporter, to act on postsynaptic receptors. Amphetamine also reduces NA reuptake via the transporter, so enhancing the action of the released NA.*

These drugs, especially amphetamine, have important effects on the central nervous system that depend on their ability to release not only noradrenaline, but also 5-HT and dopamine from nerve terminals in the brain. An important characteristic of the effects of indirectly acting sympathomimetic amines is that marked tolerance develops. Repeated doses of amphetamine or tyramine, for example, produce progressively smaller pressor responses. This is probably caused by a depletion of the releasable store of noradrenaline. A similar tolerance to the central effects also develops with repeated administration, contributing to the liability of amphetamine and related drugs to cause dependence.

Actions

The peripheral actions of the indirectly acting sympathomimetic amines include bronchodilatation, raised arterial pressure, peripheral vasoconstriction, increased heart rate and force of myocardial contraction, and inhibition of gut motility. They have important central actions, which account for their significant abuse potential and for their limited therapeutic applications. Apart from ephedrine, which is still sometimes used as a nasal decongestant because it has much less central action, these drugs are no longer used for their peripheral sympathomimetic effects.

Inhibitors of noradrenaline uptake:

Reuptake of released noradrenaline by NET is the most important mechanism by which its action is brought to an end. Many drugs inhibit NET, and thereby enhance the effects of both sympathetic nerve activity and circulating noradrenaline. NET is not responsible for clearing circulating adrenaline, so these drugs do not affect responses to this amine.

The main class of drugs whose primary action is inhibition of NET are the *tricyclic antidepressants*, for example **imipramine**. These drugs have their major effect on the central nervous system but also cause tachycardia and cardiac dysrhythmias, reflecting their peripheral effect on sympathetic transmission. **Cocaine**, known mainly for its abuse liability and local anaesthetic activity, enhances sympathetic transmission, causing tachycardia and increased arterial pressure (and with chronic use, cardiomyopathy and cardiac hypertrophy). Its central effects of euphoria and excitement are probably a manifestation of the same mechanism acting in the brain. It strongly potentiates the actions of noradrenaline in experimental animals or in isolated tissues provided the sympathetic nerve terminals are intact.

The main sites of action of drugs that affect adrenergic transmission are summarised in Fig. 2.

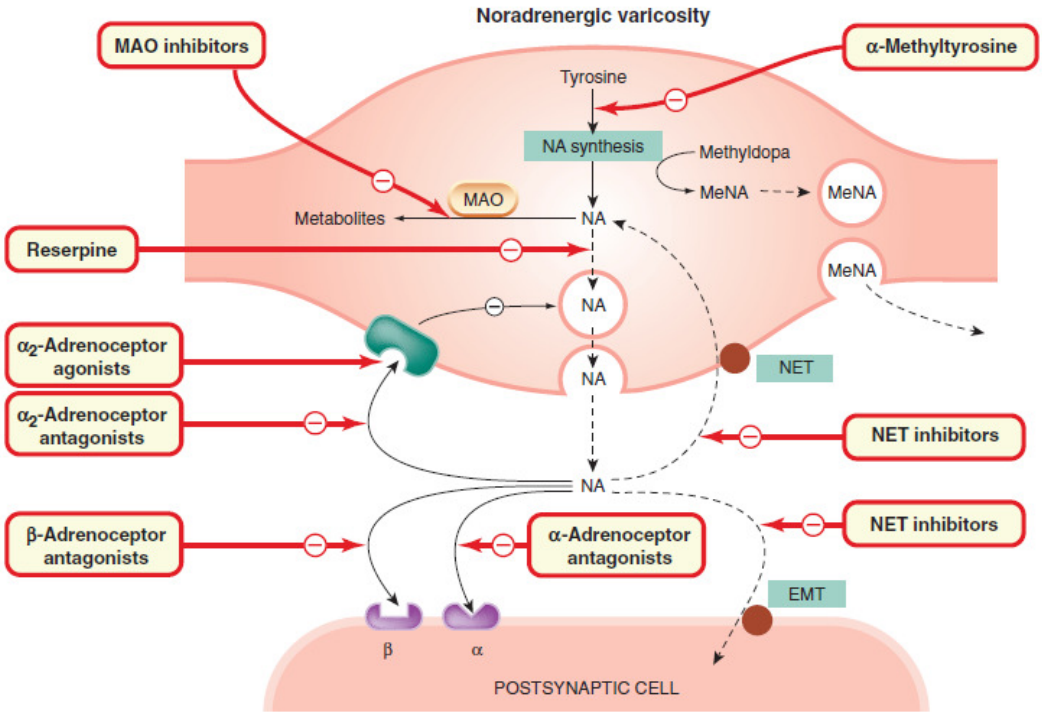


Figure 2: *Generalised diagram of a noradrenergic nerve terminal, showing sites of drug action. EMT, extraneuronal monoamine transporter; MAO, monoamine oxidase; MeNA, methylnoradrenaline; NA, noradrenaline; NET, neuronal noradrenaline transporter.*