Clinical Pharmacology and Drug Development

Pharmacodynamics, Mechanisms of Drug Action

Module 2 Topic 3

Pharmacodynamics

Pharmacodynamics is the study of the biological and therapeutic effects of drugs

- What drugs do and how they do it
- The nature and mechanism of drug actions

Mechanisms of Drug Action

Drug Action

- Curing a disease
- Only relieving symptoms

- Physical activity
- Chemical activity
- Enzyme interaction
- Inhibition of Ion channels
- Replacing chemical substances that the body lacks
- Drug-receptor interaction
- Acting on microorganisms invading the body

Mechanisms of Drug Action

- **Physical activity**
  - Some drugs act by virtue of their physical properties
  - For example, adsorption of toxins by charcoal or osmotic changes induced by certain laxatives
- **Chemical activity**
  - Some drugs produce an effect due to their chemical properties
  - For example, neutralization of stomach acid by antacids or combating acidosis by sodium bicarbonate

Mechanisms of Drug Action

- **Enzyme interaction**
  - Enzymes regulate the rate of chemical reactions
  - NSAIDs inhibit the enzyme Cyclooxygenase (COX). This stops conversion of Arachidonic acid to Prostaglandins that mediate the inflammatory response
  - Some drugs act as **false substrates** for an enzyme. For example, Fluorouracil replaces uracil so that DNA synthesis gets blocked and hence, no cell division
  - Some drugs may cause enzyme Induction e.g. increase in metabolism of other drugs by Barbiturates due to induction of CYP2B enzyme system in liver

Mechanisms of Drug Action

- **Enzyme interaction (contd)**
  - Cyclooxygenase Inhibitors for pain relief, particularly due to arthritis (aspirin; ibuprofen)
  - HMG-CoA Reductase Inhibitors for hypercholesterolemia (atorvastatin; pravastatin)
  - Angiotensin Converting Enzyme (ACE) Inhibitors for high blood pressure, heart failure, and chronic renal insufficiency (lisinopril, ramipril)

Mechanisms of Drug Action

- **Inhibition of Ion channels**
  - Many drugs inhibit ionic movement across excitable cell membranes e.g. Nifedipine blocks calcium channels, Sodium Channel Blockers suppress cardiac arrhythmias (lidocaine, amiodarone)
  - This is achieved by inhibition of enzyme activity usually by drug interaction at a receptor site

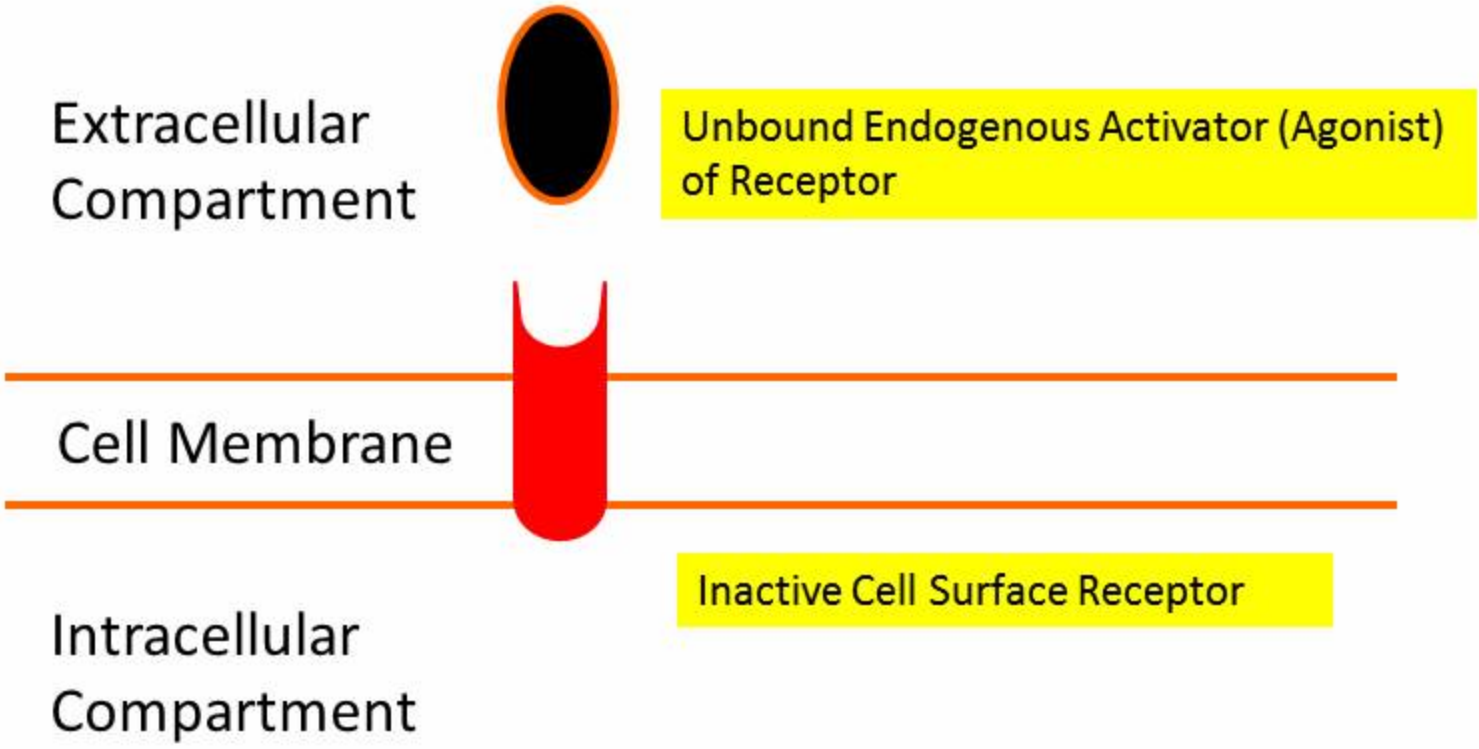
Mechanisms of Drug Action

- **Replacing chemical substances that the body lacks**
  - The body requires sufficient levels of certain chemical substances to function normally
  - A lack of **vitamin C** causes a condition called **scurvy**, lack of **vitamin D** in children leads to **rickets**, and **iron** deficiency results in **anaemia**
  - Low levels of **thyroid hormones** leads to hypothyroidism or **goiter** and a less **insulin** secretion results in a type of **diabetes mellitus**

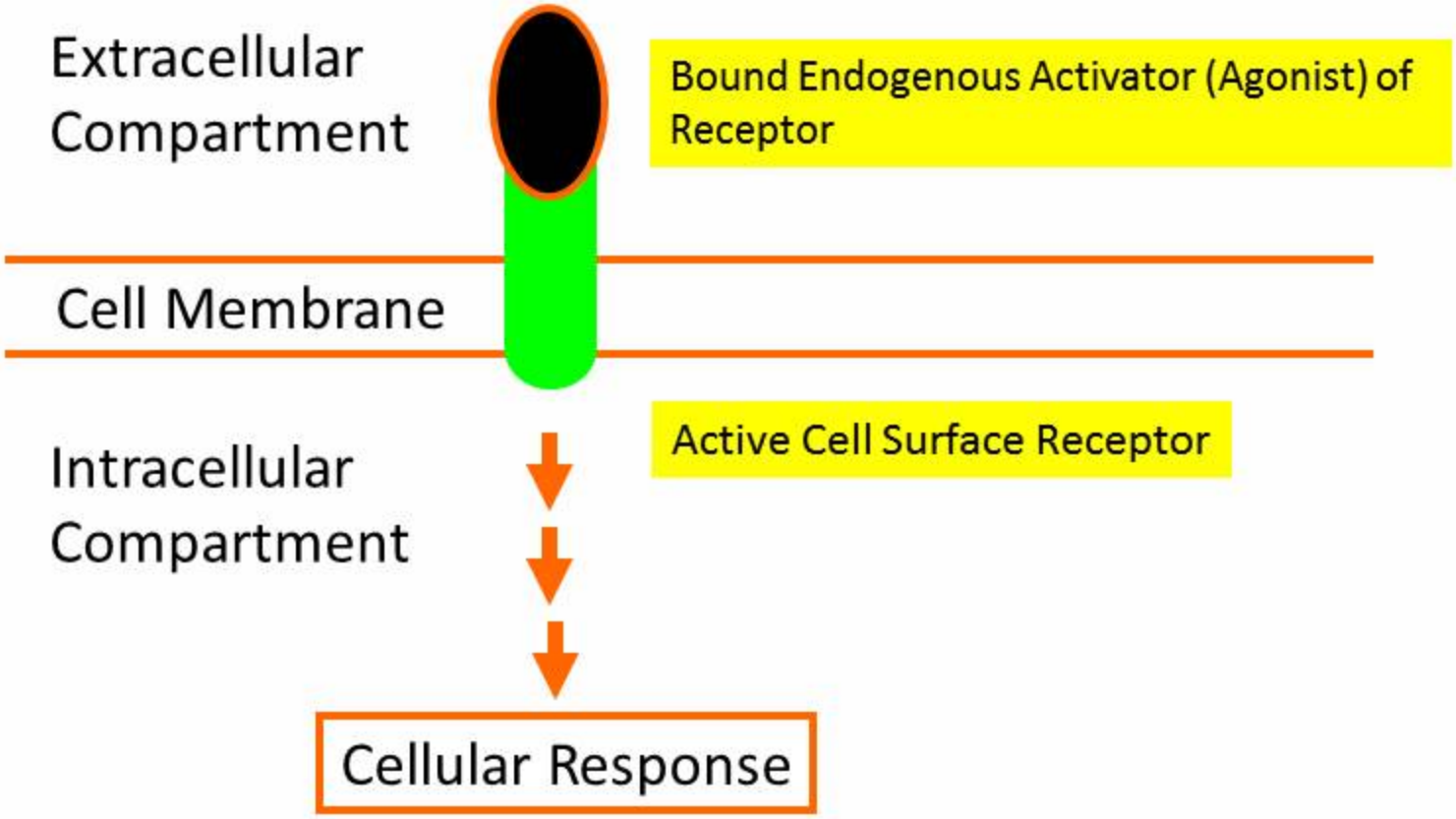
Mechanisms of Drug Action

- **Drug-receptor interaction**
  - **Receptors** are specialized element of a cell or a tissue such as proteins, enzymes, or lipoproteins
  - ***Agonists*** - *d*rugs that bind to receptors and add to the effect of the body's natural chemicals thereby enhancing cellular response are called
  - ***Antagonists*** - drugs that bind to receptors and prevent the body's natural chemicals from binding to the receptors thereby blocking the cell response are called

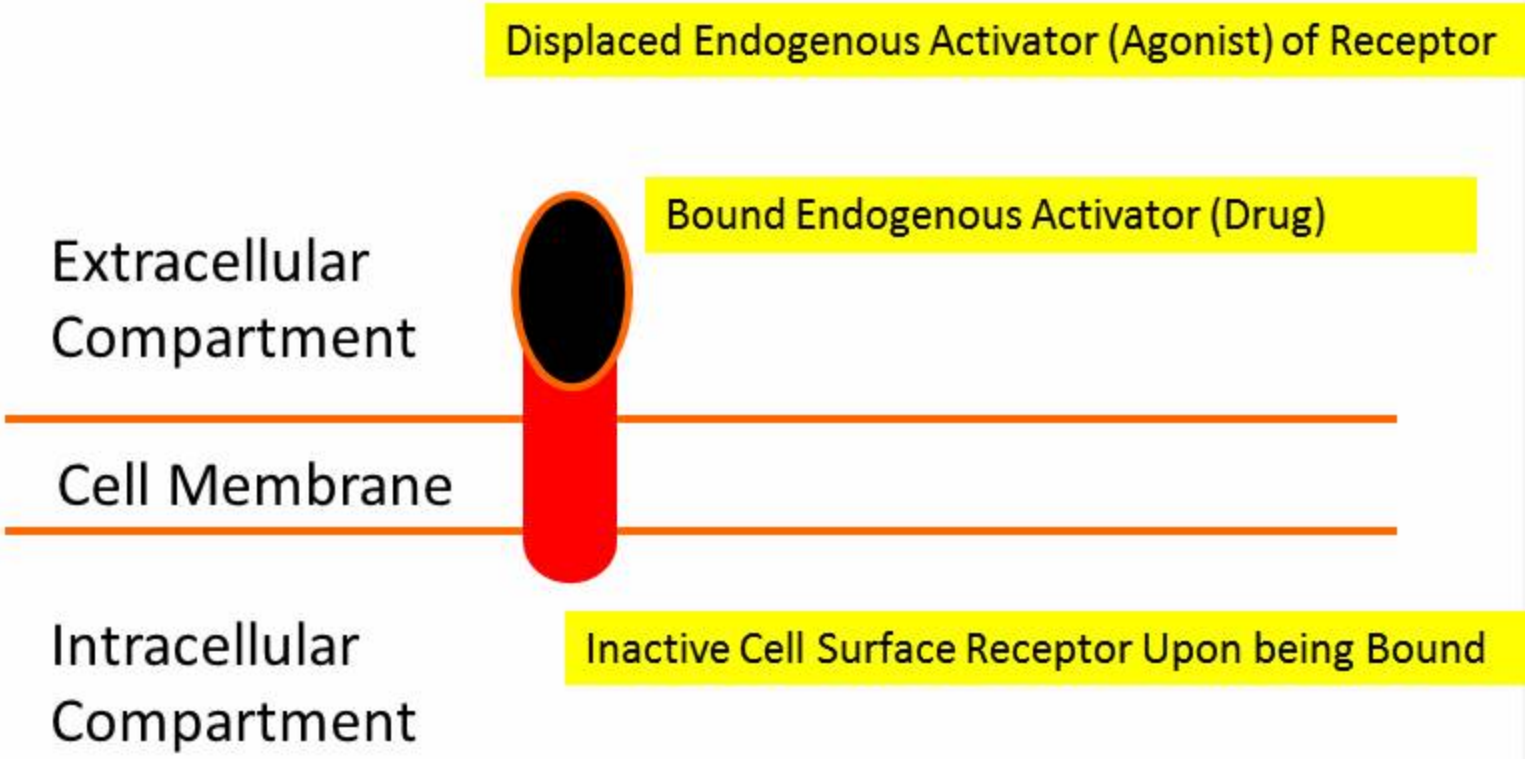
Drug-receptor interaction



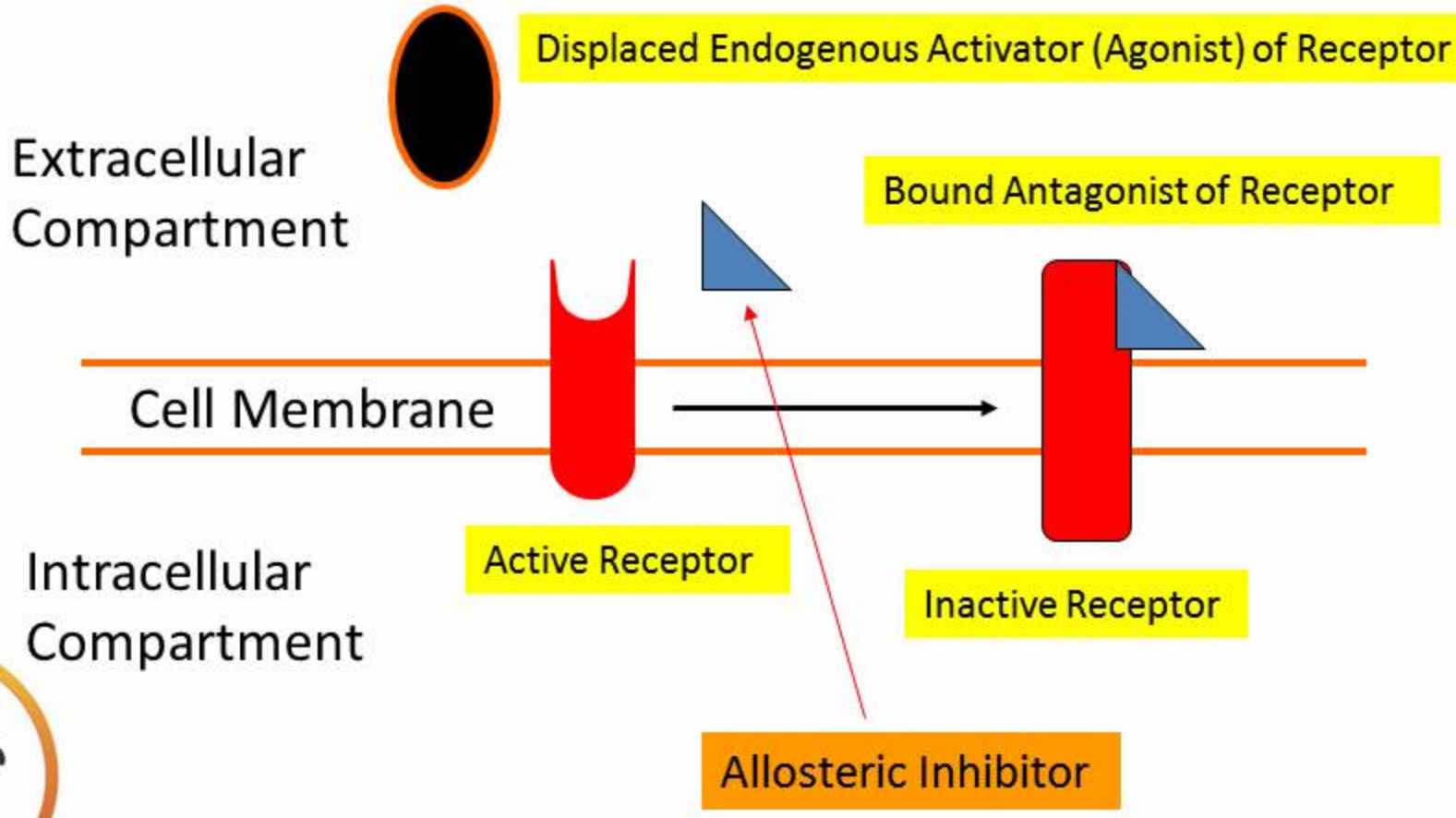
Drug-receptor interaction



Drug-receptor interaction



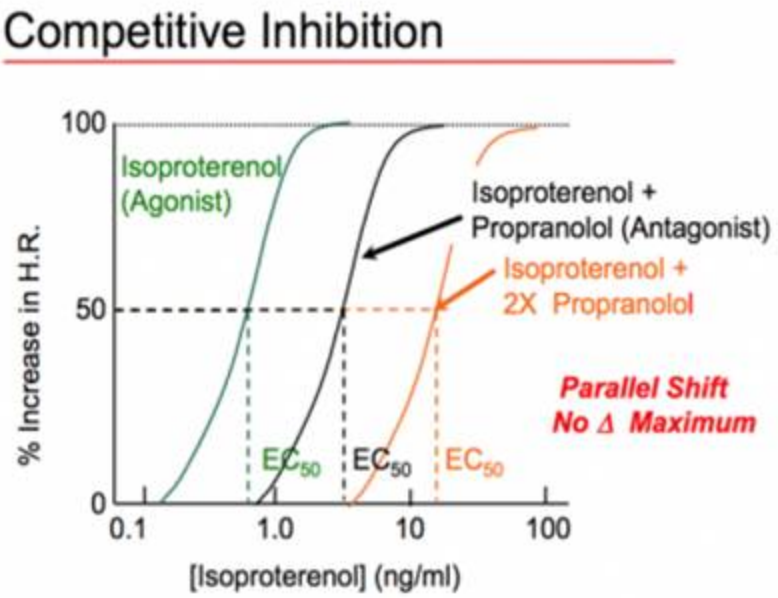
Drug-receptor interaction



Mechanisms of Drug Action

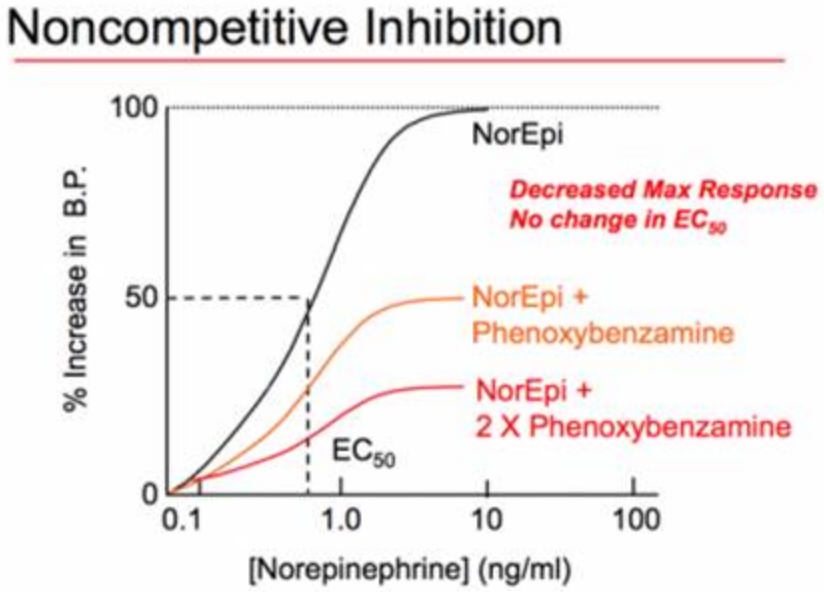
- **Competitive antagonist** competes with an agonist for the receptor site
- **Noncompetitive antagonist** binds to a site other than the agonist-binding site (called the allosteric site) of the receptor
- **Irreversible antagonist** binds permanently to the receptor binding site by forming a chemical bond that cannot be overcome by an agonist

Mechanisms of Drug Action



Competitive Antagonism, where both the agonist (Isoproterenol) and the antagonist (Propranolol) bind reversibly to the same receptor subtype (β-adrenoceptor). In the presence of the competitive antagonist, the dose-response curve is shifted to the right in a parallel manner

Mechanisms of Drug Action



Non-competitive antagonism. Phenoxybenzamine binds irreversibly (with covalent bonds) to α-adrenergic receptors. This reduces the fraction of available receptors, and reduces the maximal effect that can be produced by the agonist

Mechanisms of Drug Action

Physiological antagonism involves drug activation of two different compensatory mechanisms that exist to maintain homeostasis

- For example, the effect of **norepinephrine** to increase blood pressure via **stimulation of α-adrenergic receptors** can be antagonized by administration of **acetylcholine**, which causes vasodilation by **stimulating muscarinic receptors**, resulting in the release of nitric oxide from the arteriolar endothelium
- Acetylcholine and norepinephrine exert their effects through different receptors and signal transduction pathways, which produce opposing effects (e.g. vasodilation vs vasoconstriction). They therefore "physiologically" antagonize each others effects without interacting with the same receptors

Mechanisms of Drug Action

Pharmacokinetic antagonism occurs when one drug accelerates the metabolism or elimination of another

- For example, phenobarbital-induced enzyme induction increases the metabolism of the anticoagulant coumadin

Mechanisms of Drug Action

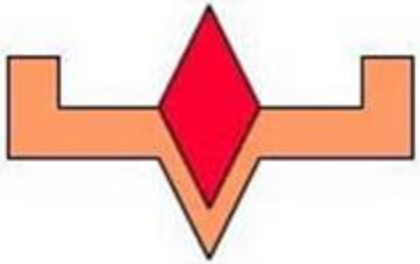
- **Partial agonist** is a drug which does not produce maximal effect even when all of the receptors are occupied by it.
- **Mixed agonist / antagonist** or a **selective receptor modulator (SRM**) is a type of drug that has different effects in different tissues
  - For example, Tamoxifen is a widely used SERM in the treatment of breast cancer

Partial agonist

- **Buprenorphine** - an opioid partial agonist that produces significant analgesic effects by stimulating opioid receptors
  - Yet has a much lower risk for producing life-threatening respiratory depression as compared to a full agonist such as morphine in case of overdose
- **Acebutolol** - "beta blocker" that has additional "intrinsic sympathomimetic activity" (ISA)
  - Behaves as partial agonist at β-1 receptors, ISA results in a neutral effect on heart rate and cardiac output when the sympathetic nervous system is not activated i.e. at rest
  - Competitive antagonist effect blunt the increase in heart rate when the sympathetic system is activated during times of stress or exercise

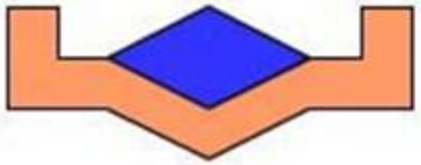
Mechanisms of Drug Action

Full Agonist



Complete conformational change leading to full activation

Partial Agonist



Partial conformational change leading to partial activation

Antagonist

No Conformational change, no activation

Mechanisms of Drug Action

- **Intrinsic activity** (**IA**) or **efficacy** refers to the relative ability of a drug-receptor complex to produce a maximum functional response
- **Affinity** is a measure of the ability of the drug to bind to its molecular target
- **Potency** is the amount of agonist needed to elicit a desired response and is proportional to both efficacy and affinity
- **EC_{50}** is a measure of the **potency** of a drug and is the concentration needed to elicit half of the maximum response of the agonist
  - The smaller the EC_{50} value, the greater the potency of the agonist and lower the concentration of drug that is required to elicit the maximum response

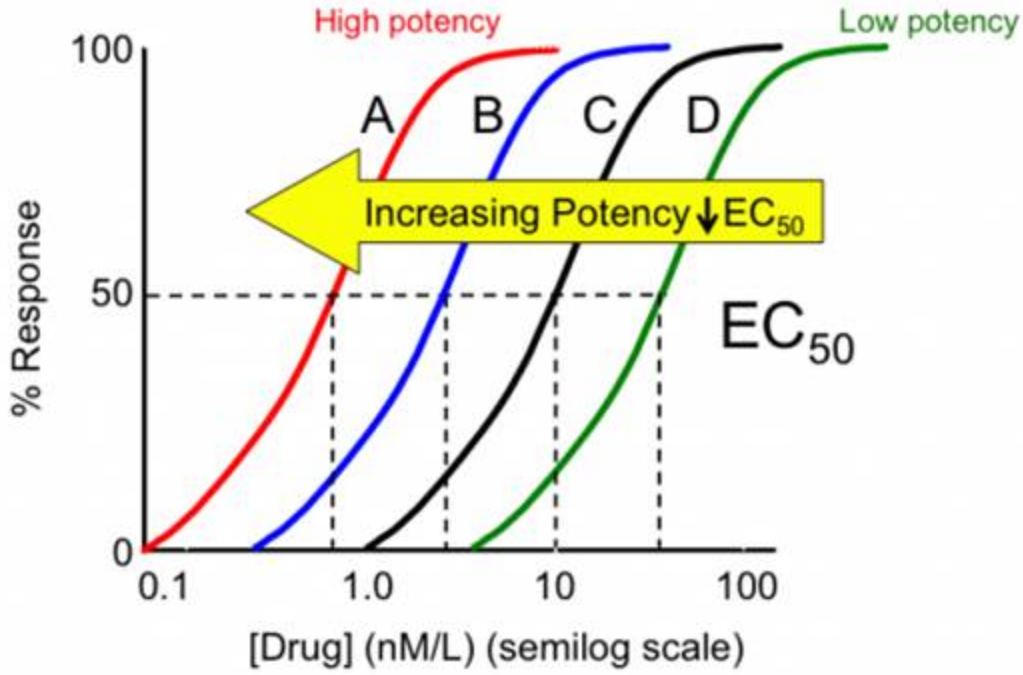
Mechanisms of Drug Action

- **Agonist** has affinity plus intrinsic activity
- **Antagonist** has affinity but no intrinsic activity
- **Partial agonist** has affinity and *less* intrinsic activity
- **Competitive antagonists** can be overcome

Mechanisms of Drug Action

- **Effective Concentration 50% (ED_{50})**
  - Concentration of the drug which induces a specified clinical effect in 50% of subjects
- **Lethal Dose 50% (LD_{50})**
  - Concentration of the drug which induces death in 50% of subjects
- **Median Toxic Dose (TD_{50})**
  - Dose at which 50 percent of the population manifests a given toxic effect

Mechanisms of Drug Action



Dose-response curves for a series of agonists (A, B, C and D) that have the same efficacy, but differ in terms of their **potency**

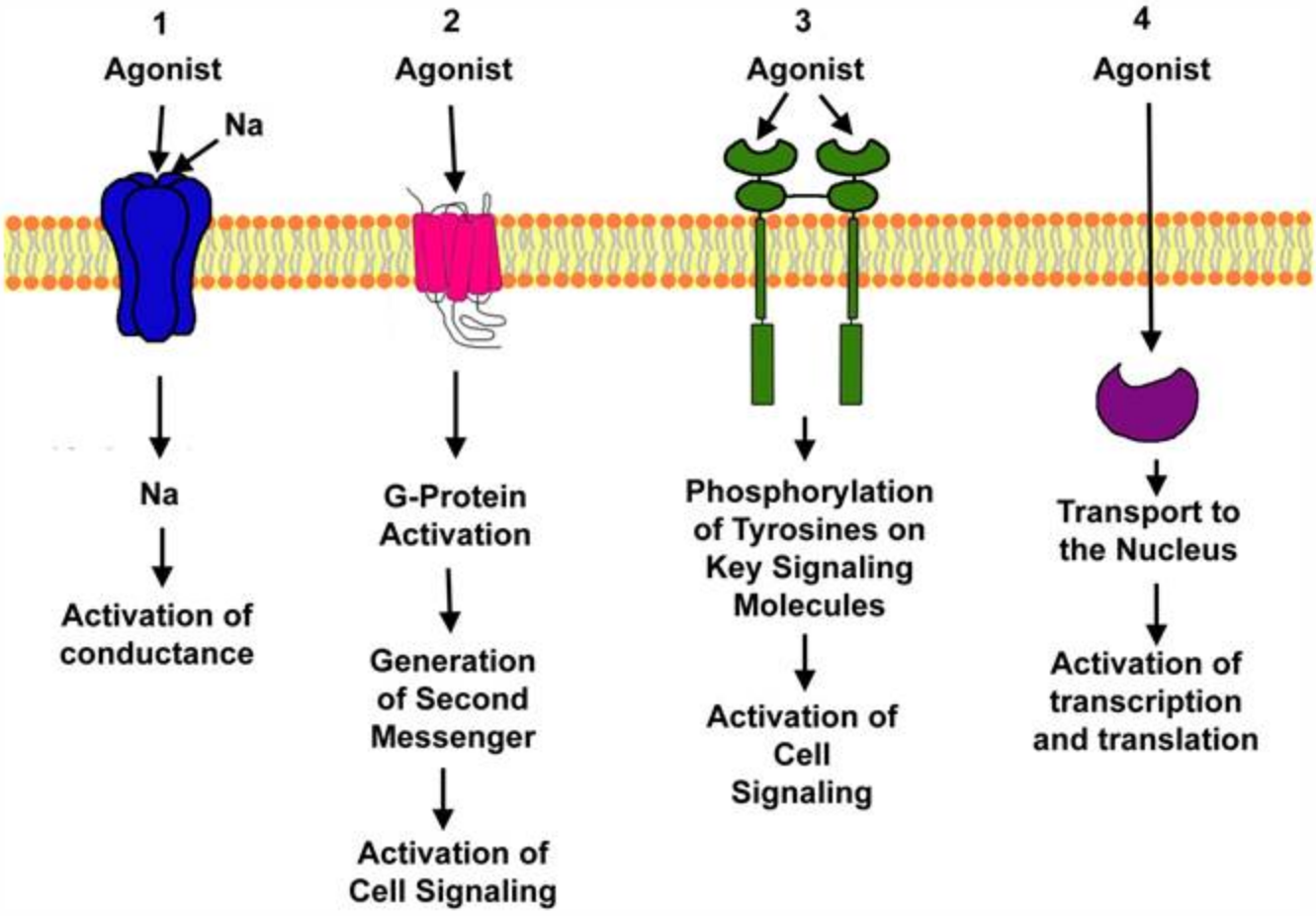
Mechanisms of Drug Action

Drug Target Receptors	Description	Example(s)
Channel-linked receptors	Coupled directly to an ion channel. Activation opens the channel, making a cell membrane permeable to specific ions. These channels are known as 'ligand-gated' because it is receptor binding that operates them (in contrast to 'voltage-gated' channels that respond to changes in membrane potential)	Nicotinic acetylcholine receptors; gamma-Aminobutyric acid (GABA) receptors
G-Protein coupled receptors	Coupled to intracellular effector mechanisms via a family of closely related 'G-proteins' that participate in signal transduction by coupling receptor binding to intracellular enzyme activation or the opening of an ion channel. Secondary messenger systems include the enzymes, adenylyl cyclase and guanylyl cyclase, which generate cyclic AMP and cyclic GMP, respectively	Muscarinic acetylcholine receptors; beta-Adrenoceptors, Dopamine receptors; 5-hydroxytryptamine (Serotonin) receptors; Opioid receptors

Mechanisms of Drug Action

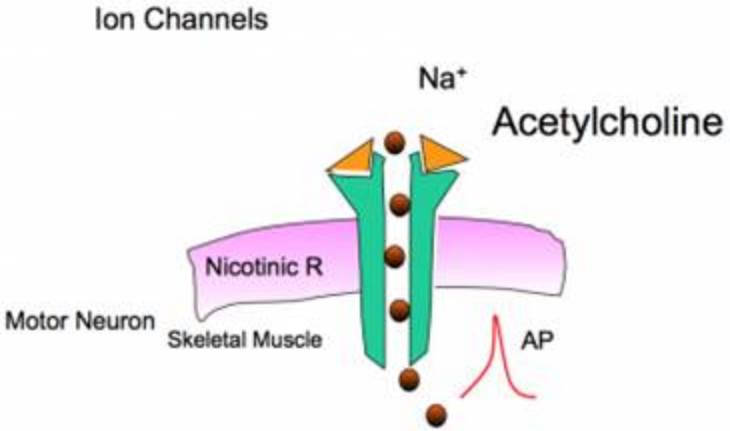
Drug Target Receptors	Description	Example(s)
Kinase-linked receptors	Linked directly to an intracellular protein kinase that triggers a cascade of phosphorylation reactions.	Insulin receptors
Nuclear hormone receptors	Intracellular and also known as 'nuclear receptors'. Binding of a ligand promotes or inhibits synthesis of new proteins, which may take hours or days to promote a biological effect.	Steroid hormone receptors; Thyroid hormone receptors; Vitamin D receptors

Mechanisms of Drug Action



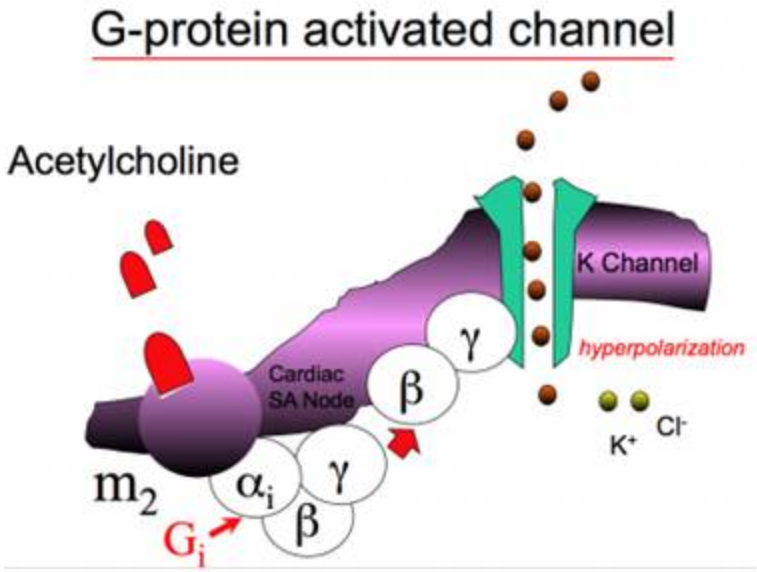
Channel-linked receptors

Ligand-gated channel



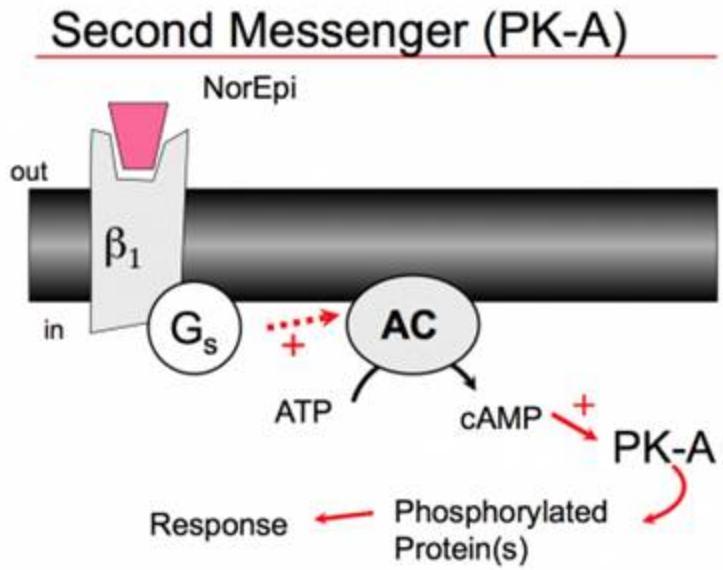
Binding of 2 molecules of acetylcholine to the nicotinic receptor/channel complex causes the channel to open. In skeletal muscle, this results in a depolarization of the membrane potential, the production of an action potential, and contraction (the biological response)

G-Protein coupled receptors



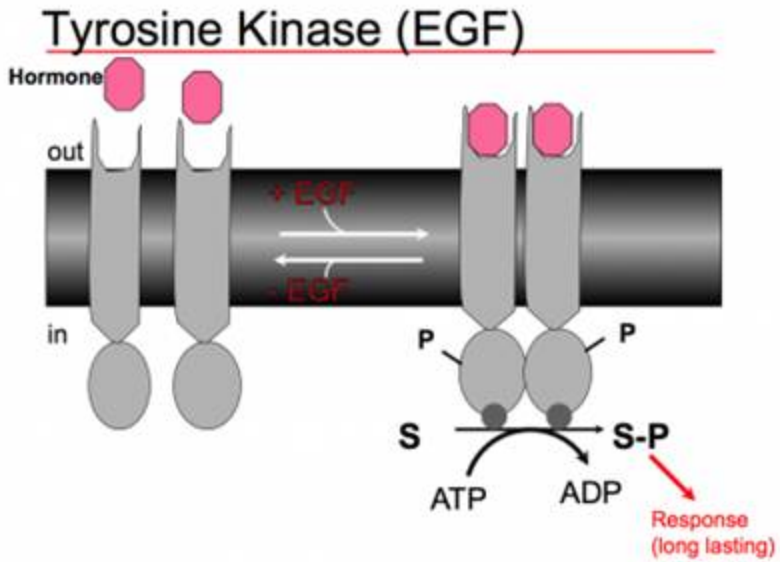
Binding of an agonist to the m2 receptor activates a G-protein (Gi) which in turn stimulates a K-selective channel to open. The increase in K permeability will hyperpolarize the membrane potential

G-Protein coupled receptors



Norepinephrine binding to beta1-adrenergic receptors stimulates adenylate cyclase (AC), which converts ATP to cAMP. cAMP acts as a second messenger to stimulate protein kinase A (PK-A), which in turn phosphorylates a variety of proteins responsible for increasing the force of contraction of heart muscle

Kinase-linked receptors



The interaction between receptors causes the tyrosine kinases to become active, resulting in auto-phosphorylation of the enzyme domains, and phosphorylation of tyrosine residues on different downstream signaling proteins (S→S-P).

The auto-phosphorylation typically results in a prolonged response to the agonist e.g. insulin that persists after the removal of the ligand from the receptor site

Mechanisms of Drug Action

- **Acting on microorganisms invading the body**
  - Infectious diseases are caused by microorganisms that attack the human body
  - Drugs destroy these microorganisms either by halting their growth or by killing them

Unconventional Mechanisms of Action

- Disrupting of Structural Proteins

  e.g. vinca alkaloids for cancer, colchicine for gout

- Being Enzymes

  e.g. streptokinase for thrombolysis

- Covalently Linking to Macromolecules

  e.g. cyclophosphamide for cancer

- Reacting Chemically with Small Molecules

  e.g. antacids for increased acidity

Unconventional Mechanisms of Action (contd)

- Binding Free Molecules or Atoms

  e.g. drugs for heavy metal poisoning, infliximab (anti-TNF)

- Being Antigens

  e.g. vaccines

- Having Unknown Mechanisms of Action

  e.g. general anesthetics

Mechanisms of Drug Action

Placebo Response

- The word ***placebo*** – Latin for ***'I will please'*** – is used to describe any chemically inert substance
- Benefit seen because the person taking it believes that it will produce good results
- '***double blind***' study in which volunteers / patients and Doctors are not aware whether they have been given the active drug or the placebo can confirm or rule out placebo effect

Mechanisms of Drug Action

Tolerance

- Tolerance is said to have developed when it becomes necessary to increase the dose of a drug to obtain an effect that was achieved earlier with a smaller dose
- It is due to changes occurring at the receptor site or due to increased metabolic inactivation of the drug resulting from enzyme induction

Mechanisms of Drug Action

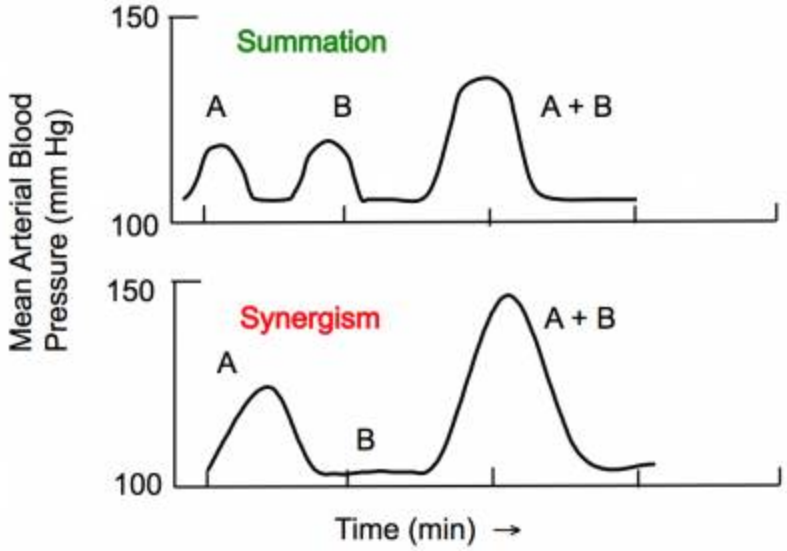
Intolerance means a low threshold of response to the pharmacological actions of a drug

Mechanisms of Drug Action

Summation and Synergism

- When two drugs with similar mechanisms are given together, they typically produce **additive** effects. This is also referred to as **summation**
- However, if the effect of two drugs exceeds the sum of their individual effects, this is referred to as **synergism** (or 'Potentiation')

Mechanisms of Drug Action



Top: Drugs A and B produce equal effects, and their effects are additive when combined i.e. Summation

Bottom: The combination of half the dose of Drug A and B produces a response greater than A or B alone i.e. Synergistic effect