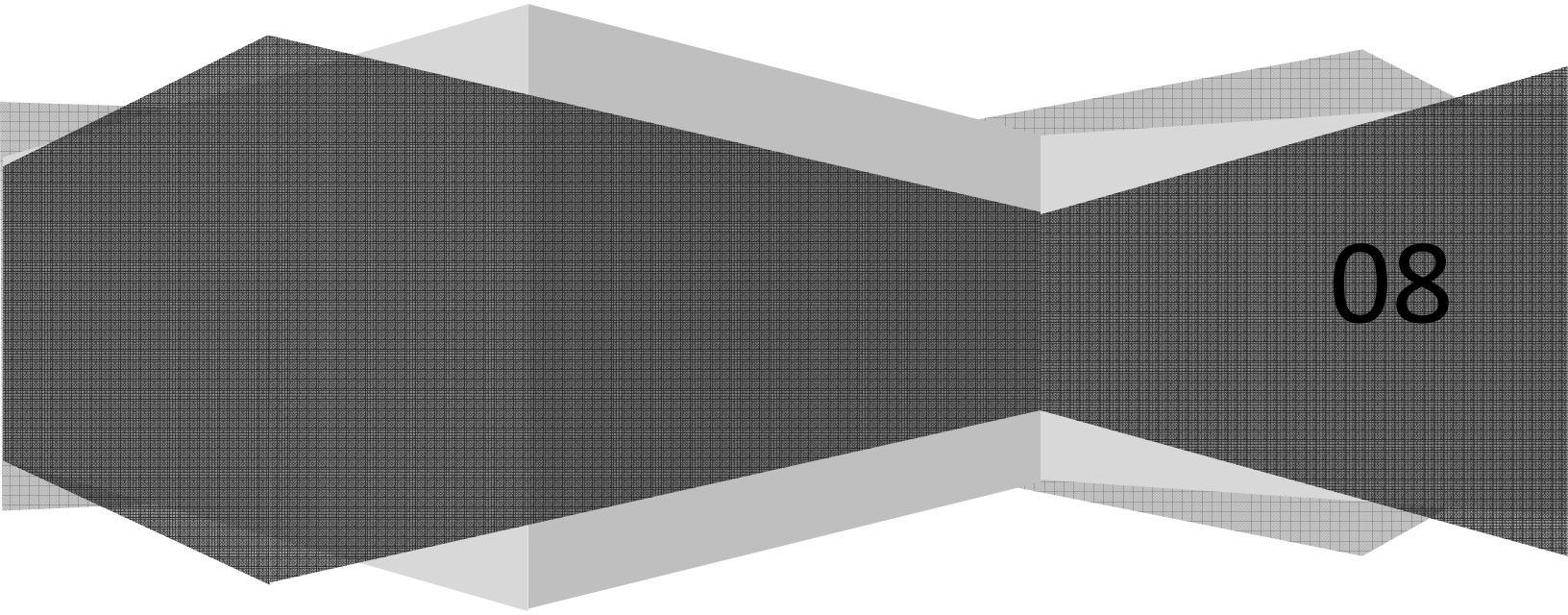
THE UNIVERSITY OF LAHORE

A GATEWAY TO PHARMACOLOGY-1

3rd Semester

Farrukh Mehmood



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A Gateway To PHARMACOLOGY-I

By

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PREFACE

This Book of Pharmacology-I has been prepared with devotion and hard work so that the students of 3rd Semester could get an easy approach to Pharmacology. This Book has been revised and referred by our Department faculty teacher of Pharmacology.

This book is made by taking guideline from Teachers, reference books and lectures delivered by teachers, which would be extremely helpful from examination point of view. The best feature of this book is that, the figures include are totally designed manually in the computer designing programs.

Now it is up to you that how you get help from it. Your suggestions with practical approach and material provided will be highly welcomed.

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DEDICATED

To

Our Teacher

Sir Saleem

Who

Teach Us,

Guide Us,

With

KEEN INTREST

GREAT EFFORTS

Contents

SOURCES

1. Lectures Delivered by Teachers
2. Lippincott's Pharmacology (3rd Edition)
   Richard D. Howland
   Mary J. Mycek

3. Basic And Clinical Pharmacology (10th Edition)
   Bertram G. Katzung

UNIT 1
Introduction to Pharmacology

Pharmacokinetics 1

Pharmacology is a Greek word derived from combination of two words.

Pharmacon = Drug
Logos = Study

"A Study in which use of medicine, actions, mechanism, uses & adverse effect of a drug on a living system."

OR

" The study of actions, mechanism, uses & adverse effects of a drug."

Pharmacology is further divided into,

Pharmacokinetics: (It is derived from Greek word Kinesis which means Movements)

"What the body does with the drug"

This refers to movement of drug in & alteration of the drug by the body including absorption, distribution, binding, storage, bio-transformation & excretion of drug
e.g.
Digoxin 70% absorbed orally, 25% bound to plasma protein localized in heart , skeletal muscle, liver, kidney, widely distributed & metabolized in liver.
Excrete out as it is in glomerulus in Kidney.

Pharmacodynamics: (It is derived from Greek word Dynamics which means Power)

"What the drug does to the body"

This include physiological & biochemical effect of drugs & their mechanism of action, macromolecular, sub-cellular organ system level.

Drug:

It is derived from French word *"Drogue*" which means a *"Dry Herb"*

According to W.H.O:

"Drug is any substance or product i.e. used & intended to be used to modify or explore physiological system or pathalogical state for the benefit of recepient (Patient)"

Branches of Pharmacology:

Medical Pharmacology:

" The Science of substance used to prevent, diagnose & treat the disease."

Toxicology:

" Which Deals with the undesireable effect of drugs on living system from individual cell to complex ecosystem"

Pharmacotherapeutics:

" Application of Pharmacodynamics information together with knowledge of disease for its prevention & cure."

Clinical Pharmacology:

The basic aim of Pharmacology is to generate data for optimum use of drug.

" It is the study of drugs in man including Pharmacodynamics, Pharmacokinetics, investigation in patients, treatment, adverse effect etc."

Chemotherapy:

" It is a treatment of systemic infection with specific drugs that have selected toxicity for the infected melagnant cells with no or minimal effects on the host cell."

Chemo-therapeutic Agents:

" These are designed to inhibit or kill invading parasites or melagnant cell & have no or minimal effect in the patient."

General Pharmacology:

Route of Drug Administration:

There are two major routes of administration.

A- Enteral
B- Parenteral

A- Enteral:

1- Oral:

Giving a drug by mouth is the most common route of administration, but it is also the most variable, & involves the most complicated pathway to the tissues.Some drugs are absorbed from the stomach; however, the duodenum is the mojor site of entry to the systemic circulation because of its larger absorptive surface.

2- Sublingual:

Placement under the tongue allows a drug to diffuse into the capillary network & therefore to enter the systemic circulation directly.Administration of an agent by this route has the advantage that the drug bypasses the intestine & liver & thus avoids first pass metabolism.

3- Rectal:

Fifty percent of the drainage of the rectal region by passes the protal circulation; thus, the biotransformation of drugs by the liver is minimized.Both the sublingual & the rectal routes of administration have the additional advantage that they prevent the destruction of the drug by intestinal enzymes or by low pH in the stomach. The Rectal route is also useful if the drug induces vomiting when orally or if the patient is already vomiting.

B- Parenteral:

Parenteral administration is used for drugs that are poorly absorbed from the GI tract, & for agents, such as insulin, that are unstable in GI tract.There are three major parenteral routes are

1-Intravascular:

Intravenous (IV) injection is the most common parenteral route. For drugs that are not absorbed orally, there is often no other choice. With IV administration, the drug avoids the GI tract & therefore, first pass metabolism by the liver. This route permits a rapid effect & a maximal degree of control over the circulating levels of the drug.

2- Intramuscular (IM):

Drugs administred IM can be aqueous solutions or specialized depot preparations often a suspension of drug in a non-aqueous vehicle, such as polyethylene glycol. Absorption of drugs in aqueous solution is fast, whereas that from depot preparations is slow.

3- Subcutaneous (SC):

This route of administration, like that of IM injection, requires absorption is somewhat slower than the IV route.Subcutaneous injection minimizes the risks associated with intravascular injection.

C- Other:

1- Inhalation:

Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract & pulmonary epithelium, producing an effect almost as rapidly as with IV injection.

This route of administration is used for drugs that are gases e.g some anesthetics, or those that can be dispersed in an aerosol. The route is particularly effective & convenient for patients with

respiratory complaints
e.g,
Asthma or chronic obstructive pulmonary disease.

2- Intranasal:

Desmopressin is administered intranasally in the treatment of diabetes insipidus; Salmon calcitonin, a peptide hormone used in the treatment of osteoporosis (Disease characterized by Weakned Bones due to low level of Calcium) is also available as a nasal spray.

3- Intrathecal/ Intraventricular:

It is sometimes necessary to introduce drugs directly into the cerebrospinal fluid.

e.g, Amphotericin B is used in treating Meningitis (Infection/ swelling characterized by bacteria or other reasons)

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.

Pharmacokinetics:

Pharmacokinetics examines the movement of a drug over time through the body. The clinician must recognize that the speed of onset of drug action, the intensity of the drug's effect & the duration of drug action are controlled by four fundamental pathway of drug movement & modification in the body.

Following are the stages of Pharmacokinetics:

1- Absorption of Drug
2- Bioavailability
3- Drug Distribution
4- Binding of Drug to Protein
5- Volume of Distribution
6- Drug Metabolism
7- Drug Elimination

1- Absorption of Drug:

"Absorption is the transfer of a drug from its site of administration to the bloodstream."
There are two generic processes of drug absorption across barrier membrane. The first barrier/type is called *"The Transcellular Process"*
Where drug mole have to go barrier cells to reach systemic circulation. Transcellular

transport is typically two step process starting with the drug uptake & end with drug efflux out of the cell.

Paracellular Transport Process:

Where the drug molecule travel between the cell (In Gaps) to reach the systemic circulation.

The Transcellular route is most important route for drug absorption except in Transdermal drug deliever where Paracellular Transport is most important.

Passage of Drug across membranes:

Passive Transport:

"It is a process by which molecules spontaneously diffuse from a region of higher concentration to a region of low concentration."

This process is passive because no external energy is needed. In this process drug molecule move forward & backward across a membrane. If the two side have same concentration of drug, forward moving molecules balanced by molecules moving back, resulting in no net transfer of drug.

Flux:

" The rate of transfer of drug from one region to another region is called flux"

Rate of Diffusion (Fick's Law):

"The drugs molecule moves from a region of high drug concentration to a region of low drug concentration."

$$dQ/dt = DAK/h \ (CGi - Cp)$$

Where

dQ/dt = Rate of diffusion
D = Diffusion co-efficient
K = Lipid water partition coefficient of a drug in biological membrane that control drug permeation.
A = Surface Area
h = Membrane thickness
CGi-Cp = Difference between concentration of drugs in G.I.T & in plasma.

Physical Factors Influencing Absorption:

i- Blood Flow to the Absorption Site:

Blood flow to the intestine is much greater than the stomach. Thus, absorption from intestine is favoured over that from the stomach.

ii- Total Surface Area available for Absorption:

Because the intestine has a surface area rich in micro villi, it has far more area than that of stomach. Thus, absorption from intestine is more efficient.

iii- Contact time at absorption Surface:

If a drug move to G.I.T very quickly as in severe diarrhea, it is not well absorbed conversely anything that delays the transport of the drug from the stomach to intestine delays the rate of absorption of the drug.

Factors Affecting Drug Absorption:

i- Lipid Solubility:

The degree of lipid solubility of drug will influence the rate of drug absorption
e.g, oil-water

Partition coefficient of this property is *" The higher the lipid solubility the greater in its transmembrane diffusion."*

ii- Molecular Size:

The diffusion coefficient is inversely related to the square root of the molecular weight. Thus, for passive diffusion small drug molecules tend to diffuse across membrane more readily than large molecule.

iii- Ionization:

Most of the drugs are weak electrolyte & exist in solution as ionized as well non-ionized. It depends upon pH of Beryllium. Non-ionized (Non-polar) lipids soluble molecules can diffuse across lipid membrane by ionized (Polar) water molecules are unable to penetrate it. The extent to which a molecule has a tendency to ionize is given by dissociation constant (Ionization Constant) Ka.

The negative logarithm constant is expressed as PKa. Generally, acidic drug have a lower PKa value & basic drug have a high PKa value. As a general principle basic drug are more ionized & less soluble in relatively acidic medium. On contrary the basic drug are more lipid soluble & more diffusible in relatively alkaline medium. Similar is the relationship between the acidic drugs & environmental pH.

i- An acid in an acid solution will not ionize.
ii-An acid in a base solution will ionized.
iii-A base in a base solution will not ionized.
iv- A base in a acid solution will ionized.

PKa is defined as
"The pH where a drug exists as 50% ionized & 50% unionized."

---> If PKa-pH = 0 Then 50% is ionized & 50% is not.
---> If PKa-pH = 0.5 Then the solution is 75% ionized & 25% unionized.
---> If PKa-pH > 1 Then the solution is 90-100% ionized & 99-100% unionized.

iv- Physiochemical nature of Drug:

Basic drugs are absorbed from the illeum, where they are in a diffusable state, while acidic drugs can be rapidly absorbed from stomach due to acidic environment but if acidic drugs are given with antacids, absorption delayed. Strong acids, strong bases or other highly polar drugs are not absorbed, as they remain ionized.

v- Gastro Intestinal Juices:

Some drugs (Polypeptides, Proteins & Carbohydrates) can be inactivated by these digestive juices & so can't be given orally
e.g, Insuline, Oxytocin, Heparin, Angiotensin & Mannitol.

vi- Intestinal Microbial flora:

Penicillinase producing intestinal bacteria & gastric HCl inactivate Benzyl Penicillin. Therefore, only acid resistant & Penicillinase resistant (Cloxacillin) are suited for oral use.

vii- First Pass Effect:

It decreases the Bioavailability of drug in systemic circulation.

viii- Gastro Intestinal Motality:

Excessively rapid motility will decrease drug absorption due to low contact time at the same time delaid passage of drugs from the stomach to the intestine as with the presence of food will delay absorption.

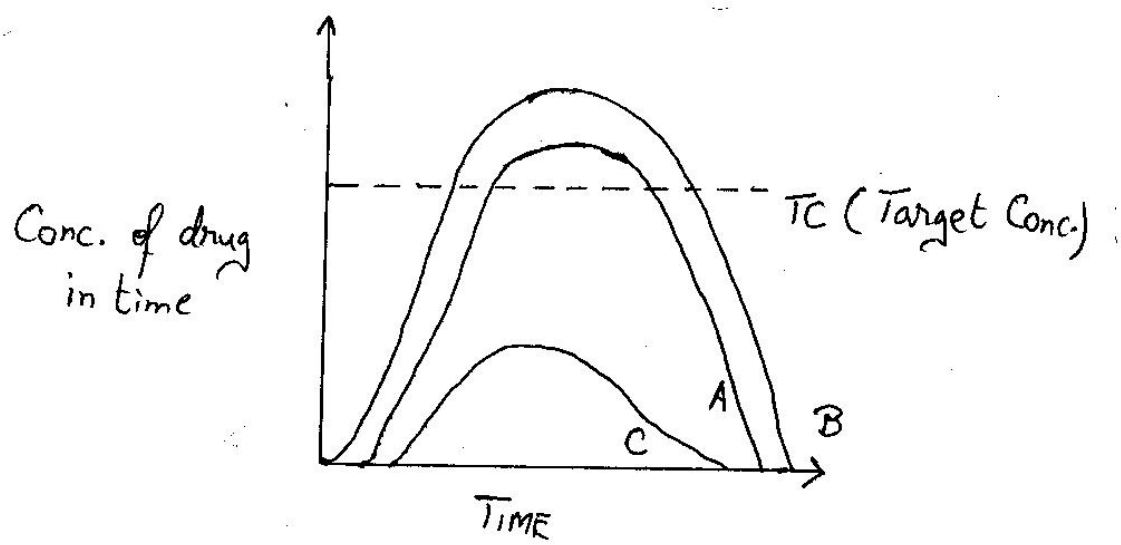
ix- Food:

Food has variable effect on rate of absorption but drug which cause gastric irritation e.g, K-supplements, Iron preparations should be given with foods.

2- Bioavailability:

"The fraction of unchanged drug reaching the systemic circulation following administration by any route."

It can be measured by area under the blood concentration drug. The blood concentration time (AUC), AUC is a common measure of extent of bioavailability for a drug given by particular route.



A = Drug rapidly & completely available
B = Only half availability of A but rate equal to A
C = Drug completely available but rate half of A

For Intra-venous dose bioavailability is assume to be equal. Orally bioavailability is less than 100%. Two main reasons are

i- Incomplete Absorption
ii- First pass metabolism

Factors that Influence Bioavailability:

There are three major factors.

i- Extent of Absorption
ii- First Pass Elimination
iii- Rate of Absorption

i- Extent of Absorption:

After oral administration drug may not be fully absorbed, this is mainly due to lack of absorption from the gut. Drug may be hydrophilic or hydrophobic, if it is hydrophilic then it cannot pass lipid cell membrane. If it is lipophilic (Hydrophobic) it cannot cross water layer adjacent to cell, this process may pump drug out of gut wall cells back into gut lumen.

ii- First Pass Elimination:

After absorption blood deliever the drug to liver. Liver is responsible for metabolism before drug reaches to systemic circulation. Liver can excreate the drug into bile. This over all process is known as First Pass Elimination. The effect of First Pass Hepatic Elimination on bioavailability is expressed as Extraction Reaction.

ER = CL (Liver)/ Q

Where

Q = Hepatic Blood flow
CL = Clearance of Liver
It is determined by site of administration & drug formulation.

iii- Rate of Absorption:

"The rate of transfer of a drug from site of administration to the blood stream is called Rate of Absorption"

Rate of Absorption depends upon the route of administration of drug.

Volume of Distribution:

"Volume of distribution relates the amount of drug in the body to the concentration of drug (C) in blood or Plasma."

Vd = Amount of drug in the body/ C

Drug with high volume of blood distribution have much higher concentration in extra-vascular tissues than in vascular compartments i.e. they are not homogenously distributed.

Clearance (CL):

"Clearance of drug is the rate of elimination in relation to drug concentration."

CL = Rate of elimination / C

Clearance may be defined with respect to drug (CLb), plasma (CLp) or unbound in water (CLu) depending on the concentration measured. The two major site of elimination are Kidney & Liver. Clearance of unchanged drug in urine represent renal clearance within liver elimination occur via biotransformation of parent drug.

Half Life:

"It is the time required to change the amount of drug in the body by one half during elimination (or during a constant infusion)."

It is useful because it indicates the time required to attain 50% steady state or to decay 50% from steady condition after change in the rate of drug administration.

3- Drug Distribution:

"The reversable transfer of Xenobiotics (Foreign Particles) from one location to another location in the body is called Distribution."

Drug distribution is the process by which a drug leave the blood stream & enters the interstecium (Extra cellular fluid) or the cells of the tissues. The delievery of a drug from one place to another depends on capillary permiability & the degree of binding of drugs to plasma & tissue proteins.

Blood flow:

The rate of blood flow to the tissue capillaries varies widely as a result the enequal distribution of cardiac output in the various organs. Blood flow to the brain, liver & kidney is greater than that to the skeletal muscles. Whereas, adipose tissue has a still lower rate of blood flow.

Capillary Permiability:

Capillary Permiability is determined by capillary structure & chemical nature of the drug. Capillary structure varies widely in term of the factors of compression of the basement membrane that is exposed by still junctions endothelial cell. In the brain the capillary structure is continous & there are no still junction. This contrast in the liver & spleen where a large part of basement membrane is exposed by large discontinous capillaries. Large plasma proteins can cross this basement membrane.

BBB:

In order to enter the brain drug must pass through the endothelial cells of the capillaries of the CNS. Lipid soluble drugs readily penetrate into the CNS. Since they can dissolve in the membrane of endothelial cells. Ionized are polar drugs generally fail to enter the CNS. Since these are enable to pass through the endothelial cell of CNS which have no still junction. These tightly juxtaposed cells on tight cells that constitute so called BBB.

Drug Structure:

The chemical nature of the drug strongly influences its ability to cross cell membrane. Hydrophobic drug, which have a uniform distribution of electrons & no net charge, readily move across most biological membrane. These drugs can dissolve in the lipids membrane & are therefore permeable to entire cell surface.

By contrast, hydrophilic drug which have either non-uniform distribution of electrons or a positive or a negative charge do not readily penetrate cell membrane. These drugs must go through the slit junction.

4- Binding of drug to Protein:

Many drugs interact with plasma or tissue protein with other molecule such as Melanin, DNA to form *"Drug Macromolecule Complex"* The formation of drug protein complex is often named as *"Drug Protein Binding."*

Drug Protein Binding may be irreversible or reversible process.

Irreversible Drug Protein Binding:

It is usually as a result of activation of the drug, in which drug attaches strongly to protein or macromolecule by covalent chemical bonding. This type of binding makes toxicity as in a case of chemical *"Carcinogenesis"*

The Hepatotoxicity of high dosage of "Acetaminophen" is due to the formation of reactive metabolite intermediates which interact with the liver proteins. Most drug bind with protein by a reversible process. In this process drug binds the protein with weaker chemical bonds, such as hydrogen bonds or Vander Waal forces.

Types of Binding Macromolecules:

Drug may bind to various macromolecular components in the blood including

i- Albumin ii- Alpha acid Glycoprotein

iii- Immunoglobulins IgG

iv- Erythrocytes

i- Albumin:

Albumin is a protein synthesized in the liver. It is the major component of plasma protein responsible for drug binding. In body albumin is distributed in the plasma & extra cellular fluid of skin, muscles & various other tissues. Interstitial fluid albumin concentration is about 60% of that in the plasma. Half life of albumin is 17-18 days. Albumin is responsible for maintaining osmotic blood pressure & for the transport of exogenous & endogenous substances. Endogenous substances includes three fatty acid, Bilurubin various hormone (Cortisone, Aldosterone, Thyroxine) & Tryptophan (Amino Acid) etc.

Albumin transport weak acidic wax
e.g, Phenyl butazone, Salicylates, Sulfonamides, Barbiturates, Tetracyclines.

ii- Alpha acid Glycoprotein (Globulins):

Alpha-1 Acid:

It is a globulin drug binding protein. The plasma concentration of Alpha-1 acid glycoprotein is low (0.4-1%). Globulin (α, β , gamma) may be responsible for the transportation of certain endogenous substances such as Corticosteroids & basic drugs
e.g, Quinine, Streptomycine, Chloramphenicol, Digitoxin, Coumarin.

Lipo-Proteins:

There are macromolecular complex of lipids & proteins & are classified according to their densities (Separation in the ultra centrifuge).

These are VLDL (Very Low Density Lipids), LDL (Low Density Lipo-Protein), HDL (High Density Lipo-Protein).

Functions:

Lipoprotein is responsible for transport of plasma lipids & may be responsible for binding of drug if albumin site become saturated.

iv- Erythrocytes:

RBC may bind both endogenous & exogenous components.
e.g. Phenytoin, Pentobarbitol, Amobarbital binds both RBC's & plasma water. RBC ,Plasma water ratio is 4-2 indicating prep rational binding to drug to erythrocyte over plasma water.

5- Volume of Distribution:

The volume of distribution is hypothetical volume of fluid into which drug is disaminated.

Water Compartment in the Body:

Once a drug enters the body from whatever route of administration, it has the potential to distribute into any one of three functionally distinct compartment of body water.

i- Plasma Compartment:

If a drug has very large molecular weight or binds extensively to plasma proteins. It is too large to move out through the endothelial slit junctions of the capillaries & thus is effectively trapped within the plasma (Vascular Compartments). As a consequent the drug distribute in a volume (Plasma) i.e. about 6% of body weight or in a 70Kg individual about 4 liter of body fluid.

ii- Extra-cellular Fluid:

If the drug has a low molecular weight but is hydrophilic it can move through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs can't move across the membrane of cells to enter the border phase inside the cells. These drugs distribute into a volume which is the sum of the plasma water & interstitial fluid which together constitute the extra-cellular fluid. This is about 20% of body weight or about 14 liter in 70 Kg individual.

iii- Total Body Water:

If the drug has a low molecular weight & is hydrophobic, it can not only move into the interstetium but it can also move through the cell membrane into the intracellular fluid. The drug therefore distribute into a volume of about 60% of body weight, or about 42 liter in a 70Kg individual.

iv- Other Sites:

In pregnancy the fetus may take up drugs & thus increase the volume of distribution.

The Apparent Volume of Distribution (Vd):

"The volume into which the drug distribute is called the apparent volume of distribution or Vd."

Determination of Vd:

The apparent volume into which the drug distribute is determined by a injection of standard dose drug. The drug is initially contained entirely in the vascular system the agent may increase from the plasma into the interstetium & into the cell causing the plasma concentration to decrease with

time assume for centricity that the drug is not eliminated from the body. The concentration of drug within the vascular compartment the total amount of drug administrated divided by the volume into which it distribute Vd.

Vd = Amount of drug in the body/ Concentration of drug in the Plasma ©

Vd = Dose/ Cp

6- Drug Metabolism:

Metabolism of bio-transformation renders lipids soluble substances to more water soluble substances & thus more readily excretable. This process primarily in liver, although the kidneys, lungs, intestinal epithelium & intestinal flora are also important metabolic sites.

The chemical reaction involves in bio-transformation of drug can be divided into phase 1 & phase 2.

Phase 1 Reaction:

These include Oxidation, Reduction, Hydrolysis which usually result in more polar compounds & greater degree of urinary excretion. Hydroxyl, Carboxyl & Amino groups are commonly added.

Phase 2 Reaction:

These involves conjugations during which polar groups are utilized for linkage to normal body constituents such as Carbohydrates & Amino Acids, Glucuronate, Glutathione, Sulphate, Alkyl groups. Conjugation usually but not always results in drug inactivation.

Bio-transformation or drug metabolism can change the drug in four different ways.

i- Change of Active drug into an Inactive Metabolite:

For instance Morphine is transformed to inactive Morphine-3-Glucuronide. (6-Glucuronide is more active)

Morphine ⟶ Morphine-6-Glucuronide ⟶ Morphine-3-Glucuronide
(Drug) (Active Metabolite) (Inactive Metabolite)

ii- Change of an Active drug to an Active Metabolite:

This reaction is finally common for instance

Acetyl salicylic Acid ⟶ Salicylic Acid (A.M)

Trimethadione ⟶ Dimethadione (A.M)

Impramine ⟶ Desipramine (A.M)

Diazepam ⟶ Desmethyldiazepam (A.M)

Chloralhydrate ⟶ Trichloroacetic Acid (I.M) ⟶ Trichloroethanol (A.M)

iii- Change of An Inactive Drug to Active one:

For instance

i- Alpha receptor antagonist & Phenoxybenzamine which needs to cyclize before it is activated.

ii- Anticancer Alkylating Agents:

Cyclophosphamide require oxidation to a varities of active metabolites such as 4-hydroxycyclophosphamide, Aldophosphamide & Acrolin. Some times both the drug & metabolites are active.

iii- Change of Active Drug to a toxic Metabolite:

For example in presence of high concentration of the analgesic Acetaminophen , N-hydroxy acetaminophen is formed which is further oxidized to reactive intermediate that can destroy & react liver cells.

Reversal of Phases:

Not all drugs undergo phase 1 & phase 2 reactions in that order e.g. Isoniazid is first acetylated (A phase 2 reaction) & then hydrolyzed to Isonicotinic Acid (A phase 1 reaction).

Enzymes in the liver are responsible for chemical changing drug components into substances known as metabolites. The family of liver isozyme known as Cytochrome-P450 are crucial to drug metabolism. These enzyme (Labeled CYP1A2, CYP2C9, CYP2D6, CYP3A4, CYP2C19) have catabolic action on substances, breaking them down into metabolites. Consequently, they also act to lower the concentration of medication in the blood scheme.

Blood in the action can occur when drug inhibits or induces a P450 that act on another drug. The metabolic rate can vary significantly from person to person & drug dosages that work quickly & effectively in one individual may not work well for another.

Factors such as genetics, environment, mutation & age also influence drug metabolism. Infants & elderly patients may have a reduce capacity to metabolize certain drugs & may require adjustment of dosage.

Cytochrome P450 (CYP 450):

CYP is short of Cytochrome P-450. P-450 is named for the fact that these are pigmented & absorb light at a wavelength of 450 mm.

CYP1A2

Where

CYP = Isoform in human origin
1 = Arabic No. Isoform's family (1st family of enzyme)
A = Sub family
2 = 2nd gene produced

7- Drug Elimination (Drug Excretion):

Administered drug in the body is allowed to produce pharmacological responses which it can produce intrinsically. This drug must be then remove from the body fluid in order to avoid its accumulation & subsequent toxicity. The process responsible for the removal of drug from the body either parent drug or its metabolite is generally known as drug excretion & also the drug elimination.

These two terms are used interchangeably into Pharmacokinetics to express the loss of drug from the body.

Drugs are eliminated from the systemic circulation by different pathways & is then excreted through one or more excretory processes
e.g. via urine, bile intestine, saliva, skin, milk & respiration.

Routes of Elimination:

Renal Excretion of Drug:

The major organ of excretion of drug is kidney. The functional unit of the kidney is Nephron in which there are three major processes to be considered.

1- Glomerular Filtration
2- Tubular Secretion
3- Tubular Reabsorption

1- Glomerular Filtration:

It is a passive process. The extent to which a drug is filtered depends on the molecular size, protein binding, ionization, polarity, kidney function in general. Glomerular filtration rate vary from individual to individual but in healthy individual the normal range is 125-130 ml/min. The filtration rate is often measured by renal clearance of inulent. Inulent is readily filtered in the glomerulus & is not subjected to tubular secretion or reabsorption.

2- Tubular Secretion:

In proximal tubule there is reabsorption of water & active secretion of some weak electrolyte but specially weak acids. As this process is an active secretion, it requires a carrier & supply of energy.

The organic acid transport mechanism excretes Hip uric acid, endogenous phenols, sulphates, glucuronides as well acidic drugs such as prabenecid, penicillin & some sulphonamides. Para-aminohip uric acid (PAH), a test substance is excreted to so efficiently by this mechanism that at propriate concentration it is completely extracted from renal plasma in a single pass. Its concentration in renal venous blood is zero.

The organic base transport mechanism continues to the elimination of basic drug (Quinidine, Cimetidine) from the body, because tubular secretion is an active process they may be competitive inhibition of the secretion of one compound by another
e.g.
The inhibition of penicillin excretion by competition with prabenecid.

When Penicillin was 1st used it was expensive & in short supply. Thus, prabenecid was used to reduce the excretion of the penicillin & thereby prolong penicillin plasma concentration. Similarly, Cimetidine competes with Quinidine for basic drug transport system.

3- Tubular Reabsorption:

In the distil tubule there is passive excretion & reabsorption of lipid soluble drugs. The drugs which are present in the glomerular filtrate can be reabsorbed in the tubule. The membrane is readily permeable to lipid so filtered lipid soluble substance are expensively reabsorbed. Highly lipid soluble drugs such as Griseofulvin reabsorption is so effective that its renal clearance is virtually zero.

Reabsorption of drug (Weak acid, weak bases) depends upon the pH of the tubular fluid (urine). When urine is acidic, weak acidic drugs tend to be removed. When urine is acidic then weak acidic are tend to be removed alternatively when urine is more alkaline weak bases are more extensively reabsorbed.
e.g.
57% of a dose of Amphetamine is excreted unchanged in the urine in acidic pH (4.5 - 5.6) compare to

about 7% in subjects with alkaline urine (pH 7.1 – 8) administration of Amphetamine with NaHCO3 has been illicitily by athletes to enhance pharmacological effect of the drug on performance as well as to make its detection by urinary screening test more difficult.

Study Questions

Choose the one best answer.

1. Which one of the following statements is correct?

   A. Weak bases are absorbed efficiently across the epithelial cells of the stomach.
   B. Co administration of atropine speeds the absorption of a second drug.
   C. Drugs showing a large Vo can be efficiently removed by dialysis of the plasma.
   D. Stressful emotions can lead to a slowing of drug absorption.

2. Which one of the following is true for a drug whose elimination from plasma shows first-order kinetics?

   A. The half-life of the drug is proportional to the drug concentration in plasma.
   B. The amount eliminated per unit of time is constant.
   C. The rate of elimination is proportional to the plasma concentration.
   D. Elimination involves a rate-limiting enzymic reaction operating at its maximal velocity (Vm).

3. The addition of glucuronic acid to a drug:

   A. Decrease its water solubility.
   B. Usually leads to inactivation of the drug.
   C. Is an example of a Phase I reaction.
   D. Occurs at the same rate in adults and newborns.

Correct Answers

Answer no. 1

Option D: Both exercise and strong emotions prompt sympathetic output, which slows gastric emptying. In the stomach, a weak base is primarily in the protonated, charged form, which does not readily cross the epithelial cells of the stomach. Atropine is a parasympathetic blocker of drug absorption. A large Vd indicates that most of the drug is outside the plasma space, and dialysis would not be effective. A small Vd indicated extensive binding to plasma proteins.

Answer no. 2

Option C: The direct proportionality between concentration and rate is the definition of first-order. The half-life of a drug is a constant. For first-order reactions, the fraction of the drug eliminated not the amount of drug is constant. A rate limiting reaction operating at Vm would show zero-order kinetics. First-order kinetics shows a linear plot (drug concentration) versus time.

Answer no. 3

Option B: The addition of glucuronic acid prevents recognition of the drug by its receptor. Glucuronic acid is chaged, and the drug conjugate has increased water solubility. Conjugation is a Phase II reaction. Neonates are deficient in the conjugation enzymes. Cytochrome P450 is involved in Phase I reactions.

Pharmacodynamics 2

Overview

Most drugs exert their effects, both beneficial & harmful, by interacting with receptors that is, specialized target macromolecules present on the cell surface or intracellularly. Receptors bind drugs & mediate their pharmacologic actions. Drugs may interact with enzymes, nucleic acids or membrane receptors. In each case, the formation of the drug-receptor complex leads to a biologic response, & the magnitude of the response is proportional to the number of drug-receptor complexes.

Drug + Receptor → Drug-receptor complex → Biologic effect

This concept is closely related to the formation of complexes between enzyme & substrate or antigen & antibody; these interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a specific ligand. However, the receptor not only has the ability to recognize a ligand (drug), but can also couple or transducer this binding into a response by causing a conformational change or a biochemical effect.

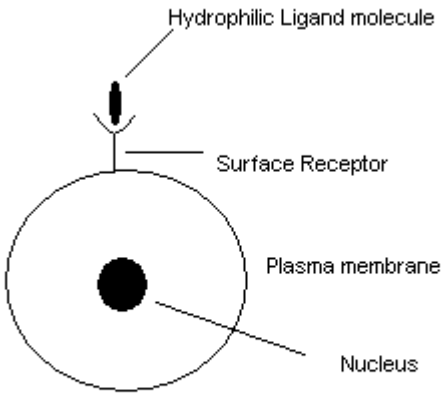
Chemistry of Receptors & Ligands:

Interaction of receptors with ligands involves the formation of chemical bonds, most commonly electrostatic & hydrogen bonds, as well as weak interactions involving van der Waals forces. These bonds are important in determining the selectivity of receptors, because the strength of these noncovalent bonds is related inversely to the distance between the interacting atoms. Therefore, the successful binding of a drug requires an exact fit of the ligand atoms with the complementary receptor atoms. The bonds are usually reversible, except for a handful of drugs that covalently bond to their targets. The size, shape & charge distribution of the drug molecule determines which of the myriad binding sites in the cells & tissues of the patient can interact with the ligand.

Major Receptor Families:

Receptor:

"Pharmacology defines a receptor as any biologic molecule to which a drug binds & produces a measurable response."



Cell Surface Receptor

Enzymes & structural proteins can be considered to be pharmacologic receptors. However, the richest sources of the therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses.

These receptors may be divided into four families:

i- Ligand-gated ion channels
ii- G protein-coupled receptors
iii- Enzyme-linked receptors
iv- Intracellular receptors

i- Ligand-gated ion channels:

The first receptor family comprises ligand-gated ion channels that are responsible for regulation of the flow of ions across cell membranes. The activity of these channels is regulated by the binding of a ligand to the channel. Response to these receptor is very rapid, having durations of a few milliseconds. The Nicotinic receptor & the Gama-aminobutyric acid (GABA) receptor are important examples of ligand-gated receptors, the functions of which are modified by numerous drugs. Stimulation of the nicotinic receptor by acetylcholine results in sodium influx & the activation of contraction in skeletal muscle. Benzodiazepines, on the other hand, enhance the stimulation of the GABA-receptor by GABA, resulting in increased chloride influx & hyperpolarization of the respective cell. Although not ligand-gated, ion channels, such as

the voltage-gated sodium channel, are important drug receptors for several drug classes, including the local anesthetics.

Ligand gated Na+ channel:

- Instead of being activated by a ligand, this channel is activated by the binding of a ligand.
- This type of Na+ channel is typically found at the neuromuscular junction.
- The channel consists of various subunits, & Ach released from the nerve terminal binds to the subunit. Binding causes a conformational twist which opens the channel, allowing Na+ to enter the muscle.

- Events at the neuromuscular junction:
    1. An action potential is propagated down a nerve fibre via voltage gated Na+ channels.
    2. At the nerve terminal, a voltage gated Ca++ channel is activated, allowing an influx of Ca++.
    3. An increase in intracellular Ca++ causes the release of Ach from the nerve terminal.
    4. Ach binds to the α subunit of a ligand gated Na+ channel of the muscle, Ach is also broken down in the synaptic cleft by ACE (Acetylcholinesterase).
    5. Opening of the ligand gated channel causes an influx of Na+ into the muscle.
    6. An influx of Na+ causes a depolarization.
    7. This membrane depolarization triggers the activation of voltage operated Na+ channels on the sarcolemma which allows the propagation of an action potential down the muscle fibre.
    8. This muscle action potential causes the release of intracellular Ca++ from the sarcoplasmic reticulum.
    9. An increase in Ca++ allows the contractile mechanisms to operate, causing muscle contraction.

G protein-coupled receptors:

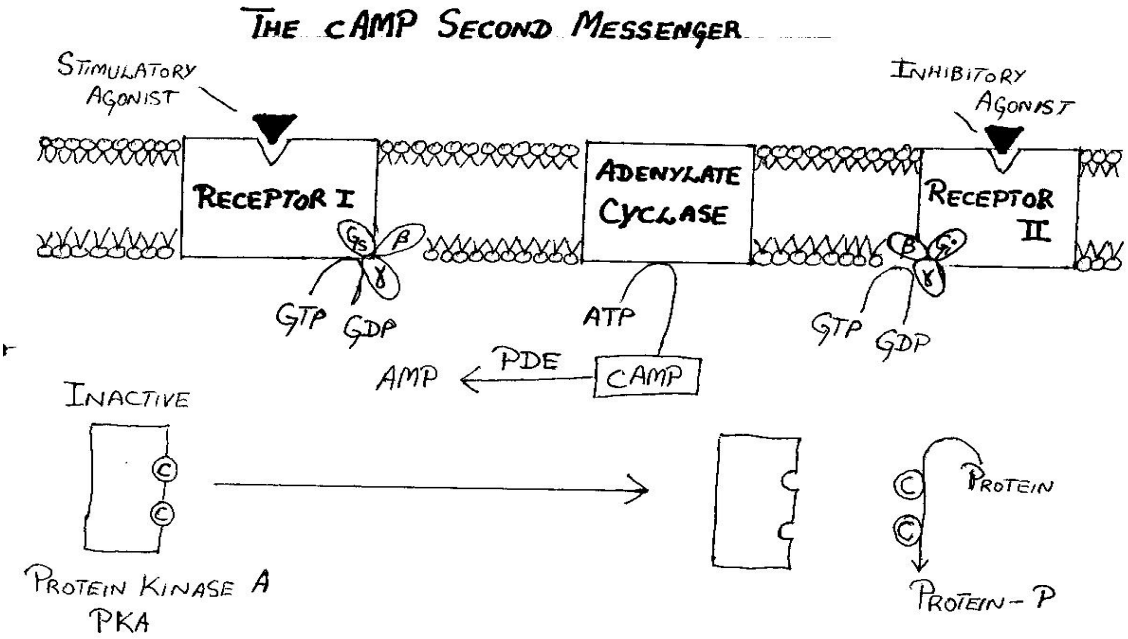
A second family of receptors consists of G protein-coupled receptors. Comprised of a single peptide that has seven membrane-spaning regions, these receptors are linked to a G protein (Gs) having three subunits, an α subunit that binds guanosine triphosphate (GTP), & a beta , Gamma subunit. Binding of the appropriate ligand to the extracellular region on the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the α-subunit. Dissociation of the G protein occurs, & both the α-GTP subunit & the beta, gamma subunit subsequently interact with other cellular effectors. These effectors are known as second messengers, because they are responsible for further actions within the cell. Stimulation of these receptors results in responses that last several seconds to minutes.

Second Messengers:

A common pathway turned on by Gs is the activation of adenylyl cyclase by α-GTP subunits, which results in the production of cyclic-adenosine monophosphate (cAMP), a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol 1,4,5-triphosphate (IP3) & diacylglycerol. These effectors are responsible for the regulation of free calcium concentrations within the cell. This family of receptors transduces signals derived from odors, light, & numerous neurotransmitters, including norepinephrine, dopamine, serotonin & acetylcholine.

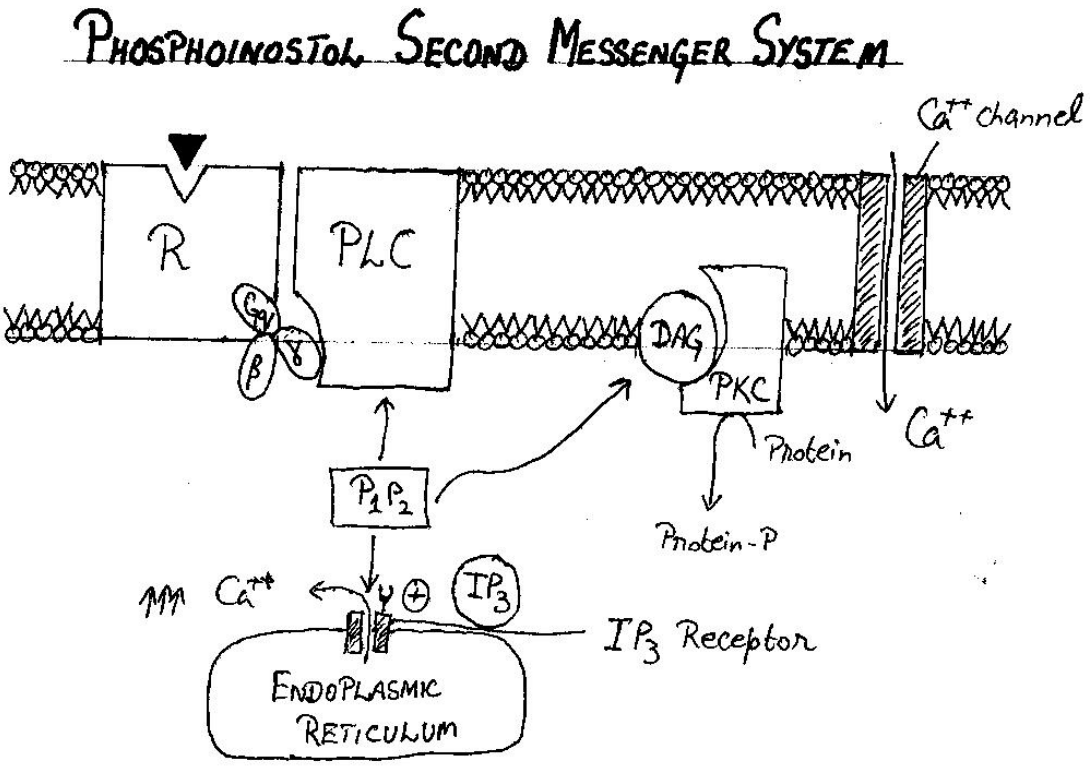
The cAMP second messenger:

1. cAMP is made by a family of membrane spannic enzyme collectively called Adenylate cyclase.
2. Receptors which associated with G-protein of Gs type stimulates adenylate cyclase. Receptors which associate with G-protein of Gi type inhibit adenylate cyclase.
3. The cAMP that is formed activates "cAMP dependent protein Kinase A" also called "Protein Kinase A" or "PKA".
4. The PKA phosphorylate other proteins (Enzymes, transporters etc) & depending on the protein increases or decreases that protein activity.



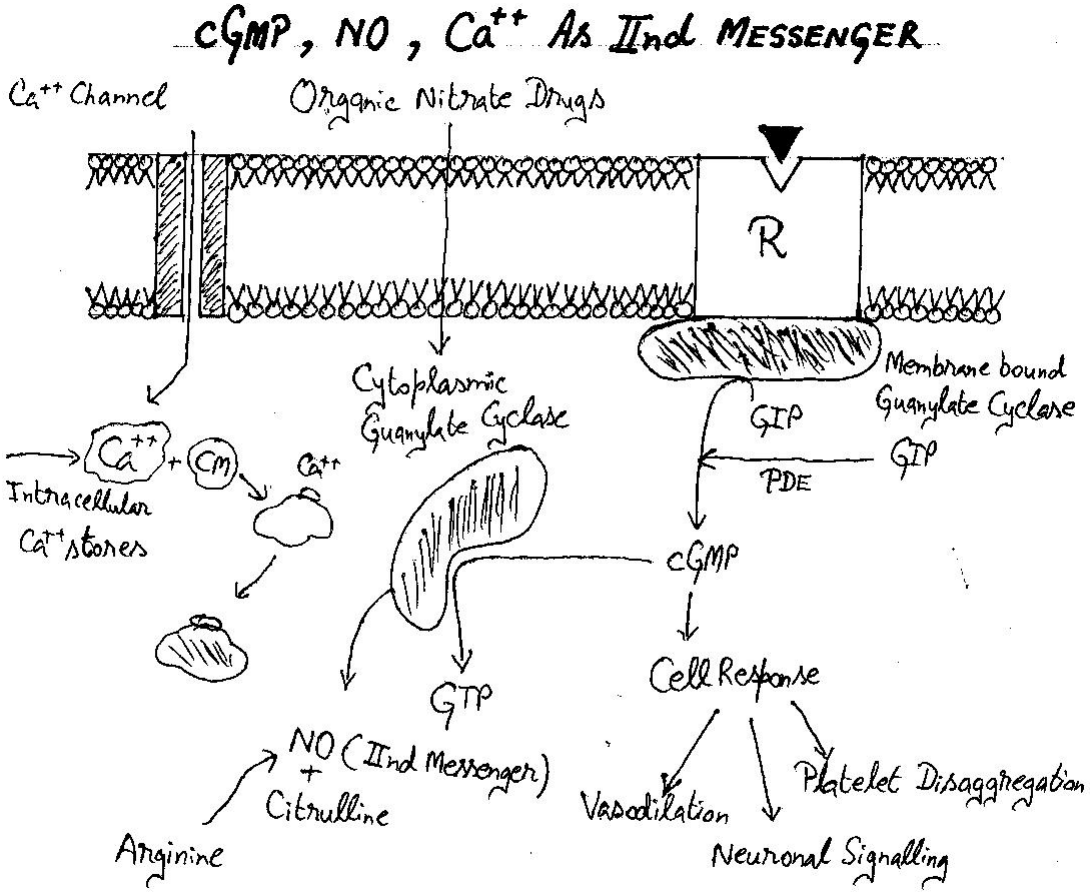
Phosphoinositol Second Messenger System: (IP3, DAG)

1. Phospholipase C (PLC) is a membrane bound enzyme that converts phosphatidyl inositol (1-4) biphosphate (P1P2) into Inositol (1,4,5) triphosphate (IP3) & diacylglycerol (DAG).
2. PLC is activated when a receptor complex activates a G-protein of Gq family.
3. The IP3 from as a plasma membrane binds to IP3 receptor on the endoplasmic membrane & release intracellular Ca++ store.
4. DAG remain membrane associated. PKC translocate from the cytosol to the membrane & becomes activated by that. Activated PKC, in term phosphorylate other proteins & alter their function state.
5. Activation of PLC system also causes the efflux of Ca++.
6. Ca++ for both extracellular & squestor intracellular sources binds one of the family of Ca++ binding proteins. This complex binds to yet other proteins & changes their functional activity.



cGMP, NO, Ca++ as Second Messenger:

1. Membrane bound Guanylate cyclase appears to be directly coupled to receptors & form cGMP from GTP when receptors become occupied.
2. NO is formed when amino acid Arginine is broken down into NO & Citrulline by Nitric oxide synthetase. It is activated by Ca++ calmodine complex.
3. NO exert its effect by activating soluble cytosolic type of Guanylate cyclase & thus increasing cGMP.
4. NO is a unique second messenger because it is membrane soluble. This allows it to diffuse near by self & increase cGMP level in those cells as well. Such a phenomena occur between vascular endothelial cell & nearby smooth muscle cells.
5. Phosphodiesterase break down cGMP & terminate its action.



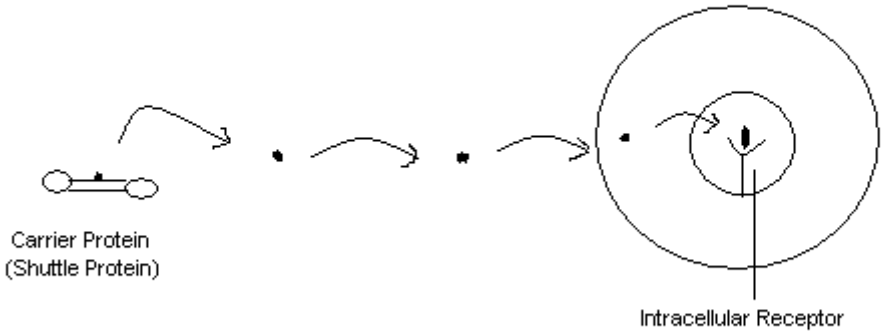
iii- Enzyme-linked receptor:

A third major family of receptors consists of those that have a cytosolic enzyme activity as an integral component of their structure or function. Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. Duration of responses to stimulation of these receptors is on the order of minutes to hours. The most common are those that have a tyrosine kinase activity as part of their structure. Binding of a ligand to two such receptors activates the kinase, resulting in the phosphorylation of tyrosine residues of specific proteins. The addition of a phosphate group can substantially modify the three-dimensional structure of the target protein, thereby acting as a molecular switch.

iv- Intracellular receptors:

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular &, therefore, the ligand must diffuse into the cell to interact with the receptor. This places constraints on the physical-chemical properties of the ligand in that it must have sufficient lipid solubility to be able to move across the target cell membrane.

For example, steroid hormones exert their action on target cells via this receptor mechanism. Binding of the ligand with its receptor follows a general pattern in which the receptor becomes activated because of the dissociation of a small repressor peptide. The activated ligand-receptor complex migrates to the nucleus, where it binds to specific DNA sequences, resulting in the regulation of gene expression.



Drug Action/ Response:

Drug acting Physiochemically

i- Osmotic precipitants
ii- Acid/base precipitants
iii- Adsorbents
iv- Protein precipitants
v- Physical barriers

Drug acting pharmacologically

i- Receptors
ii- Channels (Ca++, K+, Cl-, Na+)
iii- Enzymes
iv- Second messengers (cAMP, IP3, DAG, Ca++, cGMP)

Receptors

i- Surface Receptors

- G protein coupled receptors (GPCR's)
- Enzymes linked receptors

i- Intracellular Receptors
ii- Cholinergic Receptors

- Nicotinic Receptors (Ng , Nm)
- Muscarinic Receptors (M1, M3, M5) (M2, M4)

iii- Adrenergic Receptors

- α- adrenergic receptor (α1 adrenergic receptors, α2 adrenergic receptors)
- β- adrenergic receptor (β1 adrenergic receptors, β2 adrenergic receptors)

iv- Histamine Receptors

- H1 receptors
- H2 receptors

v- Dopamine Receptors (D1, D2, D3, D4)
vi- Serotonine Receptors
vii- GABA Receptors
viii- Glycine Receptors
ix- Glutamate Receptors
x- *Opiods Receptors*

Signal Transduction:

"The ability of a cell to change behavior in response to receptor ligand interaction."

OR

"Signal is any process by which a cell converts one kind of signal or stimulus into another."

Components of Signal Transduction:

- Signal (1st messenger)
- Receptor
- Intracellular Signaling molecules (2nd messenger)

Ligand:

"*A molecule that binds to a receptor is called Ligand."*

Types of Ligands:

1. Water Soluble Ligand
2. Lipid Soluble Ligand

1. Water Soluble Ligand:

These ligands bind to surface receptor. These are hydrophilic in nature (water loving).

e.g.

- Growth factor
- Neurotransmitter
- Peptide Hormones
- FSH
- Prolactin
- Growth Hormone

2. Lipid Soluble Ligand:

- Enter the cell
- Bind to cytoplasmic/Nuclear receptor
- Receptor ligand complex activated

- Bind to response element DNA
- Activated genes

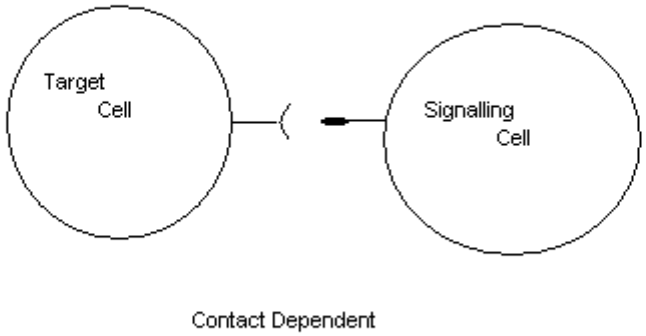
e.g.
Steroid, Cortisol, Thyroid hormone, Vitamin D, Sex hormone (Estradiol, Progesterone, Testosterone)

Signal:

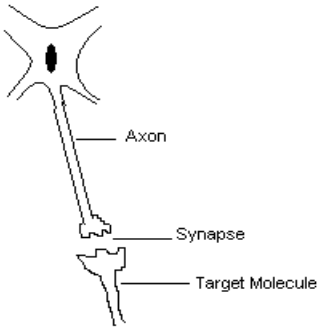
Signals are sent by organic & inorganic molecule.

Types of Signals (1st messenger):

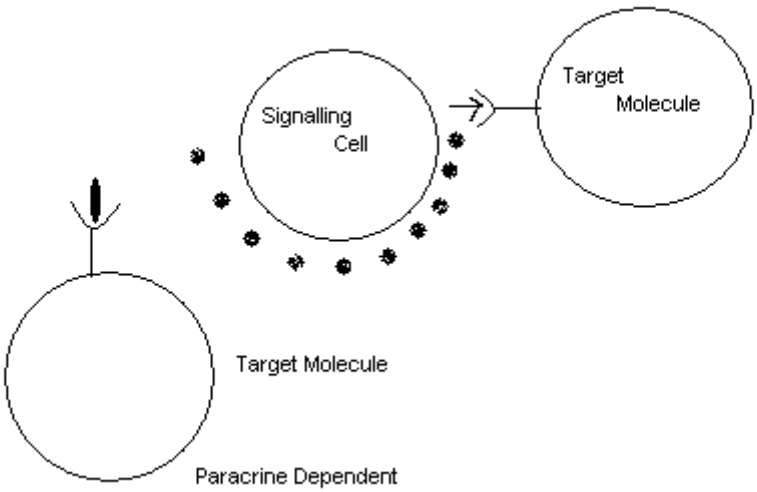
- Contact Dependent
- Neuronal Dependent
- Paracrine Dependent
- Endocrine Dependent



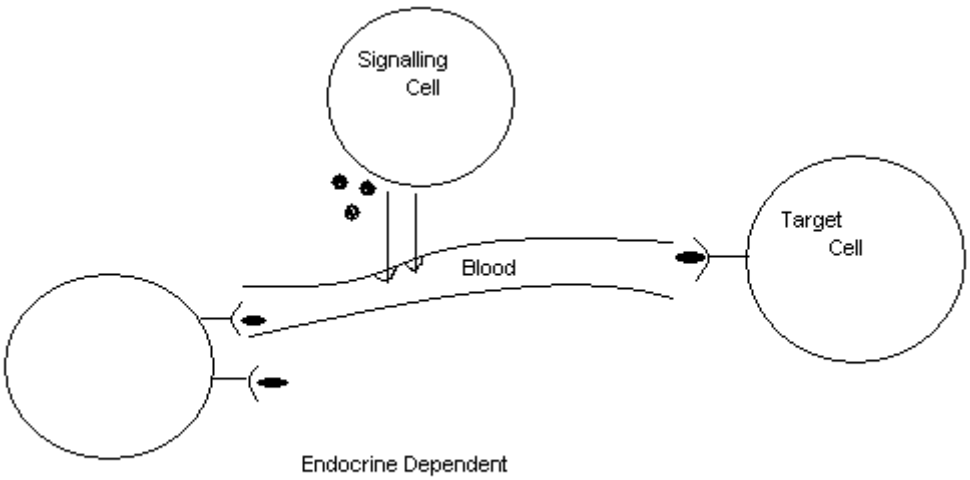
Contact Dependent



Neuronal Dependent



Paracrine Dependent



Endocrine Dependent

Drug Actions:

Process by which drugs make their action:

- Chemical
- Enzymes
- Receptors
- Ion channels
- Second messenger

Chemical action:

In this case magnesium hydroxide (an antacid) neutralizes stomach acid in the treatment of indigestion.

Drugs Acting on Enzymes:

Enzymes are biological catalyst. A catalyst is a substance that is involved in a reaction but remains unchanged itself at the conclusion of the reaction. An enzyme reacts with a substrate.

Enzymes are relatively & sometimes completely specific for a certain substrate. Pepsin is an enzyme in the stomach & is classed as proteinase. It breaks down proteins into polypeptides & amino acids. Thus pepsin is specific for proteins. It only hydrolyses peptide bonds associated with some amino acids.

Some enzymes are much more specific. Glucose dehydrogenase will act on glucose & not to the closely related sugar mannose. The specificity of enzymes resemble to that of a lock & key mechanism. Generally, only one substrate will fit into the active centre of an enzyme. When this occurs, enzymes convert a substrate into a product or products.

Competitive Inhibition:

A competitive drug can compete with the substrate for the active site of the enzyme. If the drug binds to the enzyme site it prevents binding of the normal substrate. The drug will just occupy the active site & then leaves it unchanged. Another drug or a substrate will then take its place. The action of the enzyme is slowed down by the number of times it gets occupied by a competitive substance. This substance is competitively inhibited the action of the enzyme. The substance has a similar structure to that of the normal substrate. This competitive substance is just like a key that get through the key hole turn but does not end up opening a door. More the keys are look like more time you will have to spend trying one key after another. In the situation of the enzyme, it can take much longer before being activated by the right substrate because enzyme have no memory & therefore can end up trying several times the same key.

Drugs can exert their effects by an interaction with an enzyme & therefore altering a physiological response. The neurological disorder myasthenia gravis, for example, is characterized by profound muscle weakness due to acetylcholine deficiency by acetylcholinestrease at the neuromuscular junction.

Bactrin or Septrin contain an antimicrobial drug (Sulphonamides) very similar in structure to a compound called 4-aminobenzoic acid which is essential for the synthesis of folic acid. Bacteria cannot use readily made folic acid, they must synthesize it intracellularly for their own use. Sulphonamides are competitive inhibitors of the enzyme that uses 4-aminobenzoic acid in the synthesis of folic acid. The intake of Sulphonamides will starve bacteria from folic acid.

Noncompetitive Inhibition:

Some drugs will compete for the active site but then stick there, just like the wrong key in a lock, & inactivate the enzyme. This inactivation is usually irreversible. These noncompetitive inhibitors are simple metal ions such as Arsenic or Mercury. Mercury is used in the form of mercurochrome which is toxic to bacteria & used for superficial skin infections. It is too toxic to be used internally.

Nerve gases & garden insecticides (organophosphates) are examples of noncompetitive enzyme inhibitors. They inactivate the enzyme, acetylcholinestrease. The inhibition of acetylcholinestrease prevents the breakdown of Ach & leads to prolonged receptor occupancy, increases the concentration of acetylcholine at all nicotinic & muscarinic receptors.

Drug Receptor interactions:

To produce any pharmacological effect a drug must physically interact with one or more constituents of a cell. The cell constituent that is directly involved in the initial action of a drug is called the receptor.

Receptors are macromolecular component of a cell with which a drug interacts to produce a response, usually a protein. They are proteins interacting with extra cellular physiological signals & converting them into intracellular. They are involved in chemical signaling between & within cells.

A receptor is a specialized area on the cell wall or within the cellular cytoplasm. The action of drugs is produced by its interaction with this specialized area of the membrane. Each cell membrane may have tens of thousands of receptors. Many different kinds of receptors are involved in the regulation of the various physiological activities of the body. Each neurotransmitter (e.g. Dopamine, Noradrenaline, Acetylcholine, Serotonin), each hormone (e.g. Estrogen, Insulin, Thyrotrophin), & other type of molecules (e.g. Histamine, Prostaglandins) has its own receptors.

A molecule that binds to a receptor is called a Ligand. When a ligand (Hormone, Neurotransmitter, Intracellular messenger molecule or exogenous drug) combines with a receptor, cell function changes. Each ligand may interact with multiple receptor subtypes. Activated receptors directly or indirectly regulate cellular biochemical processes (e.g. Ion conductance, Protein phosphorylation, DNA transcription).

In many cases, receptors within the cell membrane are coupled through guanine nucleotide-binding proteins (G proteins) to various effector systems involving intracellular second messenger molecules.

Receptors are dynamic, influenced by external factors as well as by intracellular regulatory mechanisms. Receptor up-regulation & down-regulation are relevant to clinically important adaptation to drugs (Desensitization, Tachyphylaxis, Tolerance, Acquired resistance, Postwithdrawal supersensitivity).

Recognition sites are the precise molecular regions of receptor macromolecules to which ligands bind. A drug may interact at the same site as an endogenous agonist (hormone or neurotransmitter) or at a different site. Agonists that bind to an adjacent or a different site are sometimes termed allosteric agonists. Nonspecific drug binding also occurs i.e. at molecular sites not designated as receptors (e.g. Plasma proteins).

A drug must attach to specific receptors either on cell membrane or within a cell. The occupation of a receptor by a drug leads to a change in the functional properties of the cell, thus producing a pharmacological response.

Drug occupation of a receptor either activates (agonist action) or inactivates (antagonist action) that receptor.

Agonists:

Agonists are drugs that have the ability to activate a receptor by binding to a receptor. They interact with receptors to alter the proportion of activated receptors, thus modifying cellular activity. They bind to & activate receptors in a dose-dependent manner until all receptors are occupied. At this point, the response plateau is reached, & increased doses of agonist do not result in increasing response. Many hormones & neurotransmitters (e.g. Acetylcholine, Histamine, and Norepinephrine) & many drugs (e.g. Morphine, Phenylephrine, and Isoproterenol) act as agonists.
Dopamine agonists: Bromocriptine, Cabregoline, Pergolide.
Serotonin antagonists: Buspirone, Dexfenfluramine, Fenfluramine.

Partial Agonists:

Partial agonists bind to the same receptors as full agonists do, & has less intrinsic activity than the endogenous ligand. At low doses they have a similar dose-dependent activity profile. However, at higher doses, receptor activation doses not increase proportionally with dose the response curve flattens far more quickly than that of a full agonist. Because partial agonists bind to the same limited number of receptors but activate them less, partial agonists reach maximal activation at a much lower level than do full agonists. It produces less than a maximal response even when it occupies all of the receptors. Partial agonists are required to interact with a large proportion of receptors to produce a maximum cellular response. In the presence of a natural agonist, a decrease in receptors is achieved but not as using an antagonist.

Inverse Agonists:

Inverse agonists bind to a receptor & produce an effect that is opposite to that of the endogenous ligand. Conventional agonists increase the proportion of activated receptors; inverse agonists reduce it.

If an inverse agonist is used to control blood pressure, the drug will actually cause a direct decrease in the blood pressure rather than just block intrinsic mechanism that cause rise in blood pressure. (Tamoxifen, Competitive partial agonist inhibitor of estradiol at estrogen receptors)

Antagonists:

Antagonists are drugs that have affinity for the same receptor sites as an agonist or partial agonist. They interact selectively with receptors but do not lead to an observed effect. They are inert & do not elicit a response. By binding to the receptor, they do block the binding of full or partial agonists, & therefore block receptor activation. They reduce the action of another substance (agonist) at the receptor site involved. Antagonists can be reversible or irreversible. Antihistamines reduce allergic symptoms by binding to histamine receptors (H1) & prevent them being stimulated by the histamine released in allergic response. Naloxone is an opoid antagonist, completely reverse symptoms of Opiods overdose by blocking the opoid receptors in the central nervous system.

Antagonism can be produced:

- Binding of an antagonist to the same site on the receptor normally occupied by the agonist. The binding of the antagonist denies the agonist occupancy of the site.
- Binding of an antagonist to a site different from that normally occupied by the agonist (allosteric site). This either prevents the agonist from binding or prevents the bound agonist from eliciting a response.

Antagonist drugs are subdivided in two major classes:

Competitive antagonism:

Competitive antagonism produce receptor blockade by competing with an agonist for the same receptor. The binding of agonist & antagonist is mutually exclusive, possibly because both agents bind to the same receptor site. The binding is reversible. (β-adrenoceptor antagonist, Propranolol, Dopamine antagonists, Chlorpromazine, Fluphenazine, Haloperidol, Serotonin antagonists, Ketanserin, Ritanserin, Ondasteron)

Noncompetitive antagonism:

Noncompetitive antagonism agonist & antagonist can be bound simultaneously, but antagonist binding reduces or prevents the action of the agonist. The binding of an antagonist is irreversible. The irreversible mechanism reduces the total number of receptors available for an agonistic action. The irreversible binding does not last forever. As cell breakdown their old receptors & synthesize new ones, the effect of noncompetitive binding subside.
(Phenoxybenzamine, irreversible a adrenoceptor antagonist).

Drug actions on ion channels:

Calcium, Sodium & Potassium are transported into or from cells in order to cause various physiological events. Sodium-Potassium transport involves enzymes that can be inhibited by drugs. In other cases, a drug can bind to channels & prevents ion movement. Like other receptors, ion channel receptors vary in different parts of the body. Drugs that have selectivity for specific channels can be made. The calcium

channel blocker, nifedipine, has action on arterioles but little action on the myocardium. The calcium channel blocker, verapamil, has the opposite effect.

Drug actions on second messengers:

There are two different systems of second messengers:

- The 3'-5' cyclic nucleotide
- The phosphoinositide

First messengers refer to hormones, neurotransmitters & Paracrine chemicals released into the extracellular fluid. These are substances that stimulate receptors. The binding of ligands (first messengers) to many cell surface leads to a short lived increase (or decrease) in the concentration of certain intracellular signaling molecules termed second messengers. These molecules includes 3'-5' cyclic adenosine monophosphate (cAMP), 3'-5' cyclic guanosine monophosphate (cGMP), 1,2-diacylglycerol (DAG), & inositol 1,4,5-triphosphate (IP3). When a first messenger stimulates a receptor it sometimes acts upon transducer substances called G-proteins.

The sequence of events that take place within the cell after the action of a first messenger depends upon which G-protein is activated. A common action of G-protein is to stimulate (or in some cases inhibit) the enzyme adenylate cyclase. Adenylate cyclase in turn converts adenosine triphosphate (ATP) to 3'-5' cyclic adenosine monophosphate (cAMP). cAMP in turn can activate many cellular functions including the activation of enzymes involved in energy regulation, cell division, cell differentiation, ion transport & ion channel function.

cAMP causes mostly an activation of regulatory protein kinases, which modulates enzymes within the cell. The actual concentration of cAMP depends on the activity of the adenylate cyclase on the one hand as well as on the activity of the phosphodiesterase on the other hand. The adenylate cyclase is located at the internal side of the cell membrane; the phosphodiesterase (there are several distinct enzymes) occur in the cytosol & are bound to the membranes of the cell, mitochondria & lysosomes. Both enzymes, adenylate cyclase & in parts phosphodiesterase, are regulated by proteins, located within the cell membrane. These proteins bind GTP & are therefore called as "GTP binding proteins" or "G-Proteins".

There are several types of G-proteins, each of which can interact with different receptors & control different effectors such as phospholipases which produce the messenger inositol triphosphate (IP3) which is an important regulator of calcium movement from intracellular stores. Some drugs can act directly on the second messenger (theophylline, used in asthma, inhibits cAMP metabolism).

Once the receptor has been activated by a ligand binding the signal has to be transported from the membrane to the cell nucleus where a specific response is initiated. In order to achieve this receptor attracts enzymes which can generate another second messenger that are in many cases derived from the lipids present in the membrane. Phosphoinositide have a prominent role in this respect & are the direct or indirect origin of many second messenger, such as diacylglycerol or inositol triphosphate & phosphatidylinositol 3,4,5-triphosphate.

The coupling of the receptor & Phospholipase C is mediated by G-proteinsin a similar manner like the cyclic nucleotides. There is no answer to the question of the

existing subtypes of the PI-system related G-protiens. There is a Gi-specific pertussistoxine (IAP) inhibiting the effects of the PI-system in mast cells, neutrophile leucocytes and adipocytes, but not in liver, heart & pancreas.

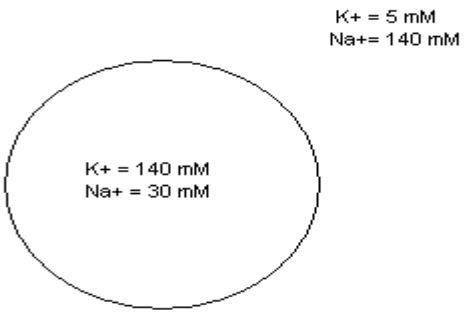
Second messenger	**G-protein**	**Receptors**	**Agonists**	**Antagonists**
cAMP	Gs	Beta 1	Epinephrine	Propranolol
		Beta 2	Norepinephrine	Cimetidine
		D1 (dopamine)	Dobutamine	
Famotidine				
		5-HT1 = S1	Isoproterenol	
		(Serotonine)	Impromidine	
		H2 (histamine)		
		Alpha2		
cAMP	Gi	D2 (dopamine)		Yohimbine
		A1 (adenosine)	Clonidine	Butyrophenones
		M2 (muscarine)		AF-DX 116
Pi	G0	H1 (histamine)	Norepinephrine	Prazosine
		Alpha 1	Thiazolylethylamine	Phentolamine
		M1 (muscarine)		Mephyramine
				Pyrathiazine
				Pirenzepine

Ion Channels (I)

- The main ion selective channels present on cell membranes are:

1. Na+
2. K+
3. Ca2+
4. Cl-

- Normal concentrations of the ions in the extracellular versus intracellular compartments



- The equilibrium potential can be calculated using the Nernst equation.
- The equilibrium potential is the membrane potential at which there is no ion flux across the membrane
- The Nernst equation is:

$$E = 615 / \text{valency} \times \log [\text{ion}] \text{ outside} / [\text{ion}] \text{ inside}$$

- Using the Nernst equation the following equilibrium potentials are obtained:
- Ek = 615 / 1 × log 5 / 140 (For Potassium)

  = -89 mV
- ENa = + 41 mV (For Sodium)
- What this mean is that membrane potential of -89 mV is required to prevent K+ from leaving the cell.

- A membrane potential of +41 mV is required to prevent Na+ from entering the cell.
- The actual membrane potential of a cell is around -60 mV. At this membrane potential, the net driving force of the ion is:
- For K+: K = Em – Ek

  = -60 - - 89 => +29
- For Na+: K = -60 - + 41

  = -101

Note:

A +ve value means a net flow out of the cell

A –ve value means a net flow into the cell

Voltage gated ion channels:

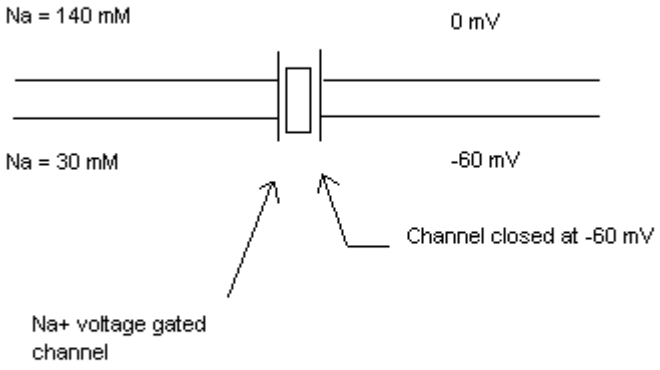
- If the Na+ channel (pore) is open, there is a massive influx of Na+ into the cell (as predicted by the net driving force of -101). This influx of Na+ is dependent on:
- The concentration gradient
- Na+ flows down its concentration gradient (from high concentration to low concentration).
- The larger the difference between the outside concentration & the inside concentration, the greater the driving force (this can be calculated using Nernst equation).
- Thus, as Na+ enters the cell, the concentration inside the cell will rise, thus reducing the concentration difference & hence the driving force. There will be a point at which no more Na+ will enter due to equilibration of the Na+ concentration (this does not occur though!).

Electrochemical Gradient:

- Na+, being a positive ion, will obviously be attracted towards the negative intracellular membrane potential.
- However, as more Na+ enters the cell, the membrane potential will rise towards a more positive value. If the membrane potential becomes positive, Na+ ions would be repelled rather than attracted towards the inside of the cell, despite its concentration gradient.

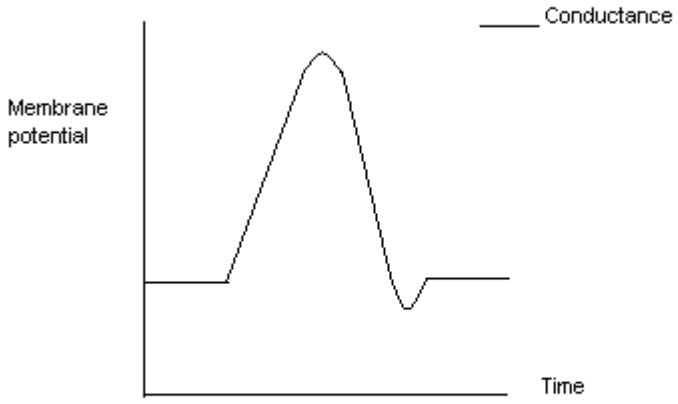
Normal Membrane Potential:

- At normal membrane potentials, the Na+ channel is closed. This channel is voltage gated; meaning that whether or not it is open or closed depends on the membrane voltage (it is closed at normal membrane potential of -60 mV).



Example of Nerve fibre:

- As an action potential comes along, a voltage sensor becomes activated & opens the Na+ channel. This allows Na+ to enter the cell causing the inside of the cell to become more positive (depolarization). The rapid influx of Na+ corresponds to a marked increase in the Na+ conductance (due to an increased Na+ permeability as a result of the channels opening).



- As the Na+ is coming in, there is also a voltage gated K+ channel. When this channel opens, K+ will rush out of the cell. As K+ leaves the cell, the membrane potential will quickly plummet towards resting membrane potential (repolarisation). The increase in K+ conductance corresponds roughly to when the Na+ conductance starts to decline.

Drugs which affect the Na+ channel:

- Local anesthetics bind to the Na+ channel & stop it from opening, hence propagation of an action potential cannot occur.
- The most common local anesthetics are

1. Lignocaine
2. Procaine
3. Cocaine
4. Benzocaine

- Common neurotoxins are:

1. Tetrodotoxin found in puffer fish
2. Saxitoxin

- The mechanism whereby the drug can stop channel opening is as follows:
- There are three forms of Na+ channel:

1. Resting (closed)
2. Open
3. Inactivated

1- Resting (closed):

At resting membrane potential, the Na+ channel is closed by the M gate. The H gate is open.

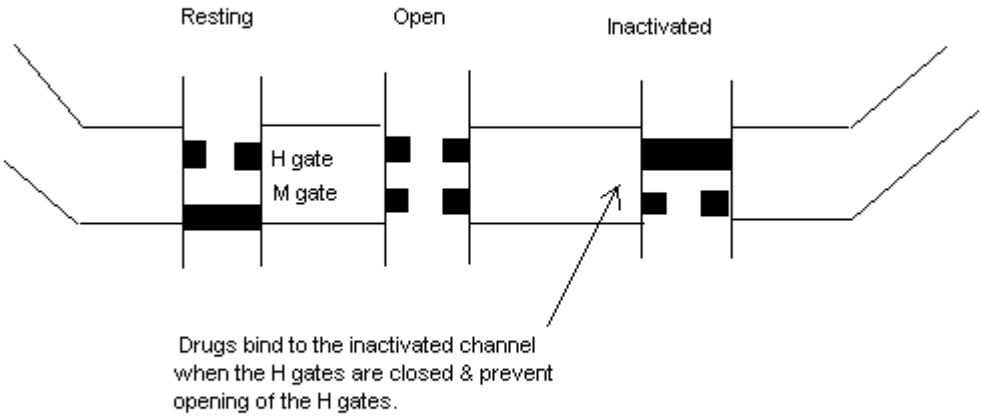
2- Open:

When there is a depolarization, the M gate opens, allowing the Na+ channel to let Na+ into the cell. Both the M gate & the H gates are open.

3- Inactivated:

- At intense depolarization, the H gates become closed. This stops any Na+ flowing in & allows for repolarisation to occur to bring the membrane back to resting potential.
- Closure of the H gates signifies an inactivated channel. The channel cannot be stimulated to open. Closure of this channel & the prevention of any Na+ influx is the basis for the relative refractory period.

- When the membrane potential returns to resting, the H gates open & the M gates close, signifying a resting channel waiting to be stimulated.



Drugs which activate the voltage gated Na+ channel- Increase the ability of the Na+ channel to open:

- Normally, the Na+ channel remains closed at resting membrane potential. When the membrane depolarizes to a threshold value, the Na+ channels open.
- Some drugs are able to make the Na+ channels open easier, thus lowering the threshold & causing increased excitability, & prolonged depolarization by preventing channel closing.
- Examples of the drugs are:

1. Scorpion toxin
2. Sea anemone toxin
3. DDT, pyrethrins
4. Veratridine

The K+ Channel:

- K+ channel allow K+ to leave the cell, making the membrane potential more negative & hence making the cell less excitable.
- There are 3 main types of K+ channels:

1. **Voltage operated K+ channel:**

The more depolarized the membrane potential, the more activated these K+ channels. Hence, when the membrane is depolarized, opening of these channels, allow K+ to leave the cell, thus repolarizing the cell, returning it back to resting states.

2. **Calcium linked K+ channel:**

When the intracellular Ca++ levels increase, this channel is opened, allowing K+ to leak out & cause a repolarization. This repolarization blocks Ca++ entry, thus bringing the cell back to a steady state.

Blockers of this channel allow Ca++ levels to rise to dangerous levels in the cell. High levels of Ca++ are cytotoxic.

Examples are:

- Apramin (found in bee venom)
- Charybdotoxin (found in scorpion venom)

3. **ATP sensitive K+ channel:**

When the ATP levels in the cell is low (as in hypoxia), K+ is allowed to leak out to shut the cell down (making it go to sleep)

High levels of ATP inhibit the channel (close the channel)

Low levels of ATP activate the channel (open the channel)

- This channel is the target of most therapeutic drugs.
- Drugs which bind to this channel & facilitate its opening are useful in hypertensive patients, K+ is allowed to leave the vascular smooth muscle cell, hyperpolarizing it & making it less excitable (relaxing it). This relaxation allows for vasodilatation to occur.
    - Some opener drugs:
        - Cromakalim
        - Diazoxide
        - Pinacidil
- An example of a drug which blocks the opening of this channel is glibenclamide.
- This drug is used as an oral hypoglycemic (lowers blood glucose)
- The β cells of the pancreas have a resting membrane potential which is maintained by the ATP sensitive K+ channel. Normally, ATP is low & the channel is open, keeping the membrane potential negative. When there is lots of glucose metabolism, ATP rises, closing the channel & allowing the β cell to depolarize (since K+ can no longer leak out).

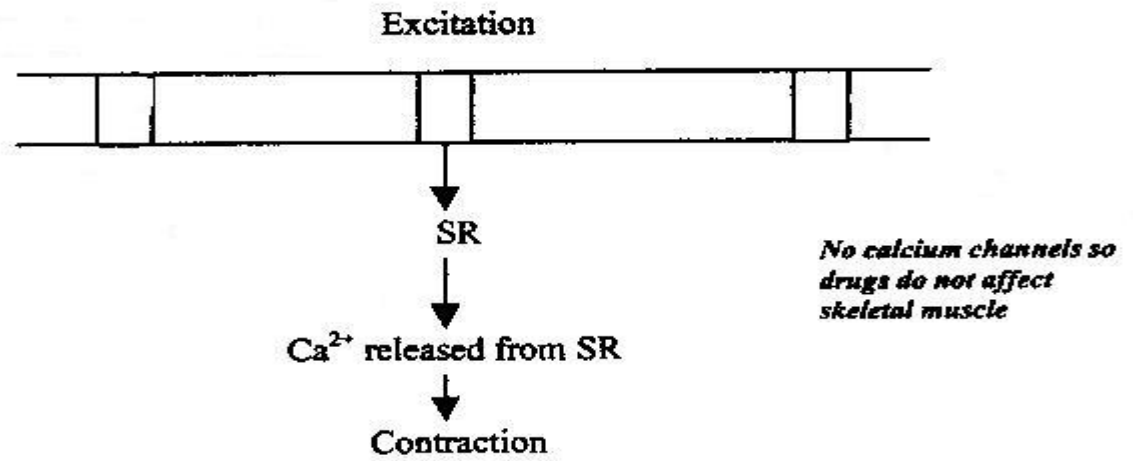
- Depolarization of the β cell allows the influx of Ca++ via a voltage gated Ca++ channel. Ca++ is required for the secretion of insulin.
- By binding to the ATP sensitive K+ channel on β cells of the pancreas, the drug mimic the effect of high ATP (it keeps the K+ channel open). The β cell is depolarized & stays that way, allowing for Ca++ influx & insulin secretion.
- The concentration required to cause this effect in β cells is very low. Glibenclamide can also be a vasoconstrictor, but the concentration to achieve this is very high. Therefore, we don't have to worry about the effects of vasoconstriction is we want to use the drug as a hypoglycemic.

ION CHANNELS II

The role of Ca++ in muscular contraction:

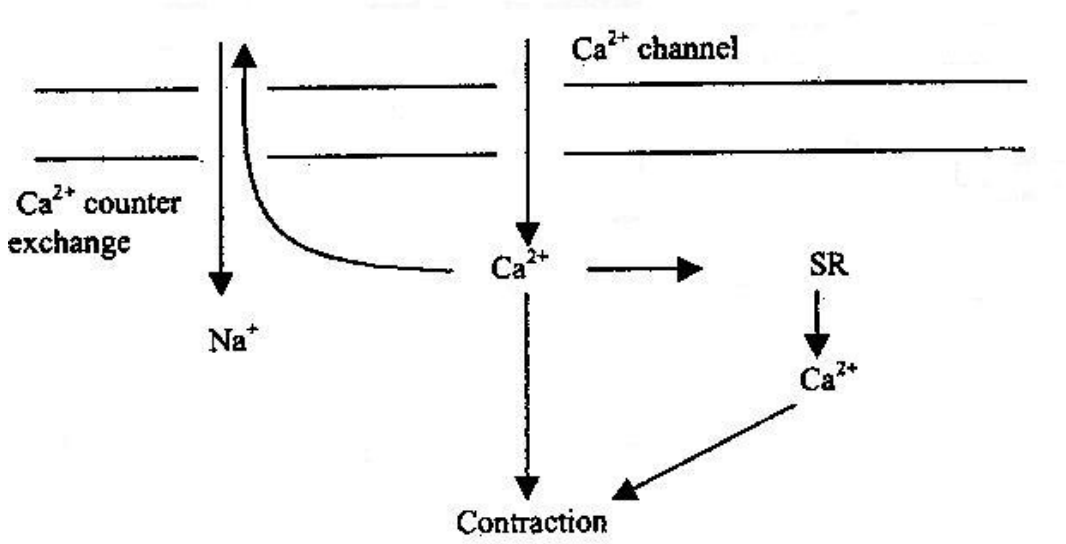
In Skeletal muscle:

- Depolarization of the muscle fibre (by the action of Ach & Na+ flow) causes the release of Ca++ stored in the sarcoplasmic reticulum. Ca++ is then able to cause contraction.
- Note that no Ca++ has been required from the extracellular fluid.
- Contraction stops when the membrane repolarizes (the Na+ channels close & K+ channels open).
- Ca++ channel blockers do not affect skeletal muscle due to the fact that skeletal muscle does not have any Ca++ channels for the drugs to work on.



In Cardiac Muscle:

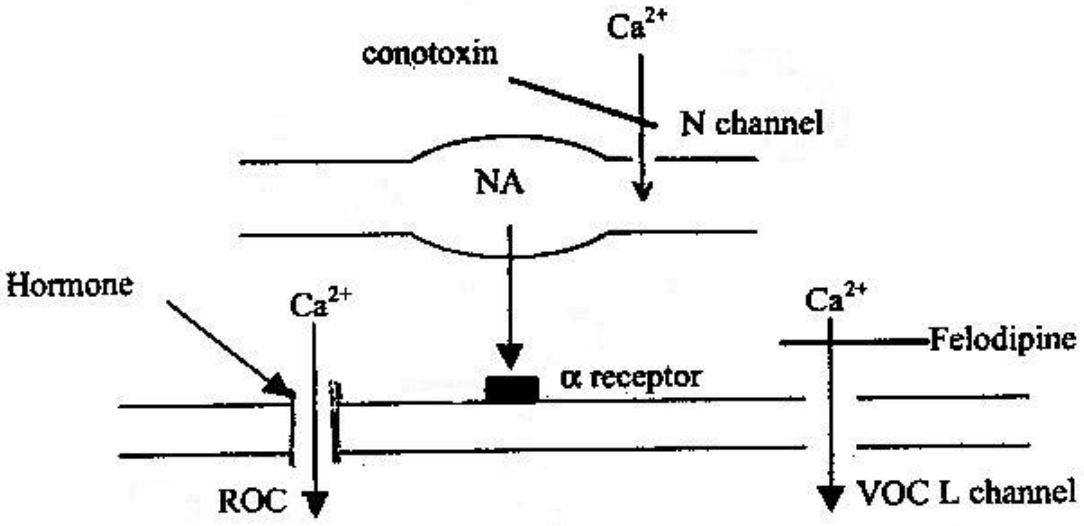
- Cardiac muscle contraction differs in many ways to skeletal muscle contraction.
- As you know, the heart has an intrinsic ability to contract, thus no stimulation is required.
- Depolarization of the cardiac muscle by the SA nodal conduction causes the opening of Na+ channels. As the membrane depolarizes further, Ca++ channels open. This allows the influx of Ca++ from the extracellular fluid. Ca++ channels stay open longer than Na+ channels; hence the action potential of cardiac muscle has a prolonged depolarization which is maintained by the influx of Ca++.
- The influx of Ca++ stimulates the sarcoplasmic reticulum to release stored Ca++. The release of Ca++ from the SR in cardiac muscle in thus voltage independent (unlike in skeletal muscle) & relies on Ca++ (Ca++ stimulates Ca++)
- After contraction, the intracellular Ca++ concentration is reduced by being sequestered by the SR or being removed out of the cell by a Na+/Ca++ counter transport.



In Smooth muscle:

- Ca++ may enter the cells via a receptor operated Ca++ channel (ROC)
- For example, Noradrenaline released from nerve terminals act on α receptors on the vessel to cause the opening of ROC channels.
- Ca++ may also enter via voltage gates Ca++ channels VOC, which open when the membrane becomes depolarized.

- Hormones may also act on receptors on the vessel to cause Ca++ release from the SR via second messenger cascades (e.g. IP3 can stimulate the release of Ca++ from the SR)



Types of Ca++ channels:

1- Voltage operated channels (VOC)

There are multiple subtypes of VOC's

i- L channel (found in the heart & blood vessels)
ii- N channel (found on neurons)
iii- P channel (found on purkinje cells, NMJ)
iv- T channel (found in the heart particularly SA node, AV node, neurons & blood vessels)

2- Receptor operated channels (ROC)

- Found in smooth muscle (e.g. blood vessels, but also anywhere else which may have smooth muscle).
- The ligands of the receptor can be adrenaline/Noradrenaline acting on the α receptor or serotonin acting on its own receptor.

3- Stretch operated channels (SOC)

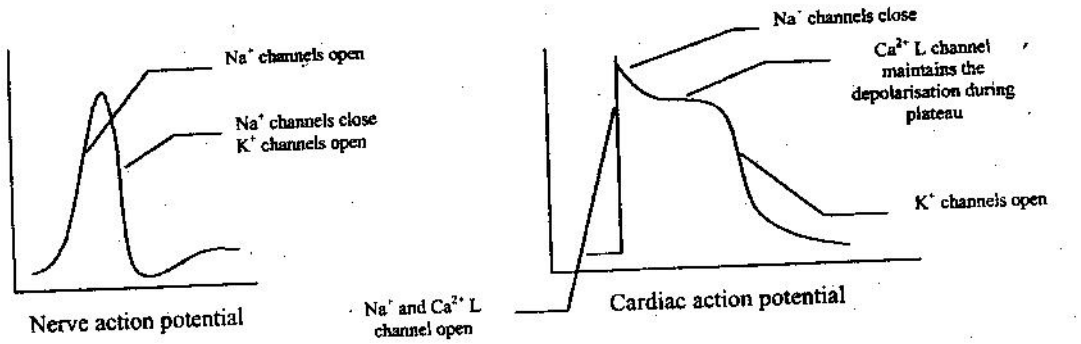
- Found on the sarcoplasmic reticulum
- Is involved in the myogenic response.

4- Second messenger operated channels (SMOC)

- Found on vascular smooth muscle.
- Open by an intracellular second messenger (e.g. IP3, cAMP).

Voltage operated Calcium Channels:

- The different subtypes of VOC's are characterized by their electrophysiological characteristics.
- In cardiac muscle or nerves, initial membrane depolarization is the result of Na+ channels opening, causing a massive influx of positive Na+ ions going into the cell, making the cell depolarize.
- In the nerve cell, as the membrane depolarizes to a certain point, the Na+ channels close & K+ channels open, allowing for K+ ions to move out of the cell, bringing the membrane potential back towards negative (repolarization).
- In cardiac muscle, the muscle potential is very different. As the membrane is depolarizing, Ca++ channels are opening as well as Na+ channels. However, when the Na+ channels close, the Ca++ channels are still open, maintaining a depolarization for longer (plateau stage), before the K+ channels open & repolarize the cell.



In the nerve, the Ca++ channel is known as the N channel.

- It opens when the membrane depolarizes at around -20 mV.
- Is stays open for 50-80 ms.
- Its conductance is 13 pS (Siemens)
- The conductance tells us about the bulk of Ca++ flowing.
- Entry of Ca++ into the nerve terminal allows the release of neurotransmitter.

5- The L-channel (Long opening)

- Found in the heart & blood vessels.
- Opens when the membrane depolarizes at -10 mV
- It stays open for > 500 ms
- Its conductance is 25 pS
- This channel is the channel predominantly responsible for the prolonged depolarization during the plateau phase in cardiac muscle.

6- The T-channel (Transient)

- Opens very early on during the depolarization, at -70 mV
- However, it is open for a very short time, 20-50 ms
- It has a low conductance of 8 pS
- Only one newly discovered has been shown to affect it – Mibefradil

The Ca++ channel blockers:

- There are 3 classes of L channel blocker drugs.

i- Dihydropyridines

- *Nifedipine*
- *Nicardipine*
- *Amiodipine*
- *Felodipine*
- *Laudipine*
- *Nisoldipine*

ii- Phenylalkylamines:

Verapamil

- Mibefradil was developed as an analogue of verapamil & is able to be a good peripheral & coronary vasodilator while having little potency in depressing the heart.
- Verapamil is a good vasodilator but has quite a strong action on the heart.

Benzodiazepines

Diltiazem

- Nifedipine was the 1st discovered L Channel blocker.
- It was found to reduce the force of contraction of the heart by reducing the plateau phase of the cardiac action potential.
- A L channel blocker can be good as a vasodilator because it will relax the smooth muscle in the blood vessels (coronary arteries included) because Ca++ entry into the cell is also required for smooth muscle contraction. However, the drug may also cause an unwanted negative inotrophic effect on the heart.

Study Questions

Choose the one best answer.

1. Which of the following statements is correct?

    A. If 10 mg of Drug A produces the response as 100 mg of Drug B. Drug A is more efficacious than Drug B.
    B. The greater the efficacy, the greater the potency of a drug.
    C. In selecting a drug, potency is usually more important than efficacy.
    D. A competitive antagonist increases the ED~50.

Correct answer = D

In the presence of a competitive antagonist, a higher concentration of drug is required to elicit a given response.

2. Variation in the sensitivity of a population of individuals to increasing doses of a drug is best determined by which of the followings?

    A. Efficacy
    B. Potency
    C. Graded dose-response curve
    D. Therapeutic Index

Correct answer = C

Only a quantal dose response curve gives information about differences in the sensitivity of individuals to increasing doses of a drug.

Unit II: Drugs Affecting the Autonomic Nervous System

The Autonomic Nervous System 3

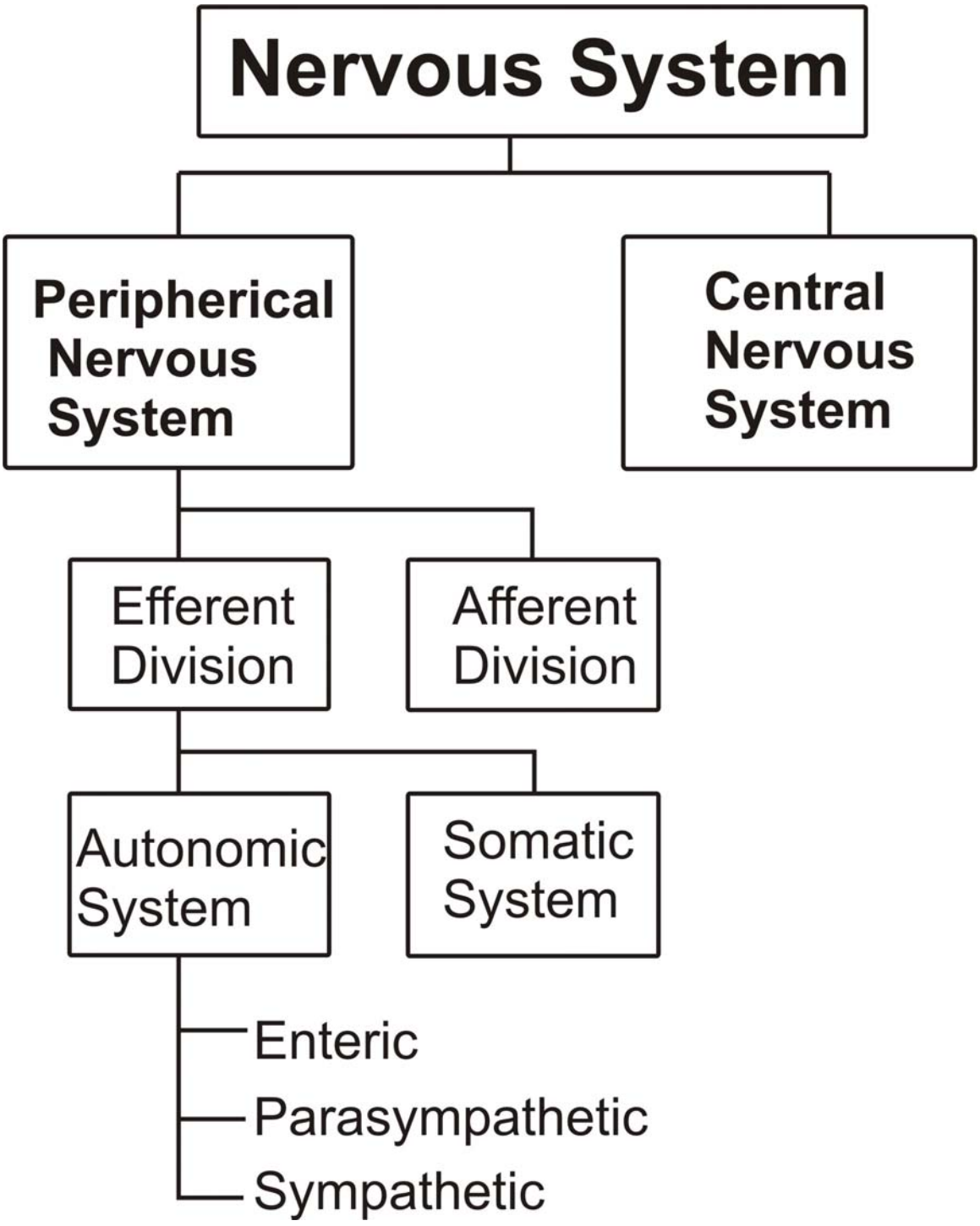
INTRODUCTION TO THE NERVOUS SYSTEM

The nervous system is divided into two anatomical divisions

1. Central Nervous System (CNS) (which is composed of the brain & spinal cord)
2. Peripheral Nervous System (which include neurons located outside the brain & spinal cord)

The peripheral nervous system is subdivided into

i) The efferent divisions (The neurons of which carry signals away from the brain & spinal cord to the peripheral tissues)
ii) The afferent divisions (The neurons of which bring information from the periphery to the CNS)


Nervous System
Peripherical Nervous System
Central Nervous System
Efferent Division
Afferent Division
Autonomic System
Somatic System
Enteric
Parasympathetic
Sympathetic

A. Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions,

i) Somatic System (involved in the voluntary control of function such as contraction of the skeletal muscles essential for locomotion)
ii) Autonomic System (involuntarily regulates the everyday needs & requirements of the vital bodily functions without conscious participation of the mind)

B. Anatomy of the autonomic nervous system

1. Efferent neurons:

The autonomic nervous system carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons. The first nerve cell is called a preganglionic neuron, & its cell body is located within the CNS. Preganglionic neurons emerge from the brainstem or spinal cord & make a synaptic connection in ganglia. These ganglia function as relay stations between the preganglionic neuron & a second nerve cell, the postganglionic neuron.

2. Afferent neurons:

The afferent neurons of the autonomic nervous system are important in the reflex regulation of this system, & signaling the CNS to influence the efferent branch of the system to respond.

3. Sympathetic neurons:

The efferent autonomic nervous system is divided into the sympathetic & the parasympathetic nervous system. Anatomically, they originate in the CNS & emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from thoracic & lumbar regions of the spinal cord, & they synapse in two cord-like chains of ganglia that run in parallel on each side of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones.

4. Parasympathetic neurons:

The parasympathetic preganglionic fibers arise from the cranium & from the sacral areas of the spinal cord & synapse in ganglia near or on the effector organs. Thus, in contrast to the sympathetic system, the preganglionic fibers are long, & the postganglionic ones are short.

5. Enteric neurons:

The enteric nervous system is the third division of the autonomic nervous system. It is a collection of nerve fibers that innervate the gastrointestinal tract, pancreas, & gallbladder, & it constitutes the “brain of the gut”. This system functions independently of the CNS & controls the motility, exocrine & endocrine secretions, &

microcirculation of the gastrointestinal tract. It is modulated by both the sympathetic & parasympathetic nervous systems.

C. Functions of the sympathetic nervous system

Sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, or exercise.

1. Effects of stimulation of the sympathetic division:

The effect of sympathetic output is to increase heart rate & blood pressure, to mobilize energy stores of the body, & to increase blood flow to skeletal muscles & the heart while diverting flow from the skin & internal organs. Sympathetic stimulation results in dilation of the pupils & the bronchioles. It also affects gastrointestinal motility, & the function of the bladder & sexual organs.

2. Fight or flight response:

The changes experienced by the body during emergencies have been referred to as the "fight or flight" response. These reactions are triggered both by direct sympathetic activation of the effector organs, & by stimulation of the adrenal medulla to release epinephrine & lesser amounts of norepinephrine. These hormones enter the blood stream & promotes responses in effector organs that contain adrenergic receptors. The sympathetic nervous system tends to function as a unit, & it often discharges as a complete system
For example, during severe exercise or in reactions to fear.

D. Functions of the parasympathetic nervous system

The parasympathetic division maintains essential bodily functions, such as digestive processes & elimination of wastes, & is required for life. It usually acts to oppose or balance the actions of the sympathetic division & is generally dominant over the sympathetic system in "rest & digest" situations. The parasympathetic system is not a functional entity as such, & never discharges as a complete system. If it did, it would produce massive, undesirable & unpleasant symptoms.

E. Somatic nervous system

The efferent somatic nervous system differs from the autonomic system in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. The somatic nervous system is under voluntary control, whereas the autonomic is an involuntary system.

CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the autonomic nervous system is an example of the more general process of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling are the release of local mediators & the secretion of hormones.

A. Local mediators

Most cells in the body secrete chemicals that act locally i.e. on cells in their immediate environment. These chemical signals are rapidly destroyed or removed; therefore they do not enter the blood & are not distributed throughout the body.
Histamine & prostaglandins are examples of local mediators.

B. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body exerting effects on broadly distributed target cells in the body.

C. Neurotransmitters

All neurons are distinct anatomic units, & no structural continuity exists between most neurons. Communication between nerve cells & effector organs occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. Uptake of Ca++ ensues to initiate docking of the synaptic vesicles & release of their contents. The neurotranmitters rapidly diffuse across the synaptic cleft or gap (synapse) & combine with specific receptors on the postsynaptic (target) cell.

1. Membrane receptors:

All neurotransmitters & most hormones & local mediators are too hydrophilic to penetrate the lipid bilayer of target-cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs.

2. Types of neurotransmitters:

Over fifty signal molecules in the nervous system have tentatively been identified, six signal compounds

- Norepinephrine
- Acetylcholine
- Dopamine
- Serotonin
- Histamine
- Gamma-aminobutyric acid

(Are commonly involved in the actions of therapeutically useful drugs.)

a. Acetylcholine:

The autonomic nerve fibers can be divided into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic. Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic & parasympathetic nervous systems.

b. Norepinephrine & epinephrine:

When norepinephrine or epinephrine is the transmitter, the fiber is termed adrenergic. In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs.

CHOLINERGIC PHARMACOLOGY 4

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1. Cholinomimetic Drugs (agents that directly enhance cholinergic function):

A. Choline esters

- Acetylcholine
- Methacholine
- Bethanechol (Urecholine)

B. Naturally occurring cholinergic stimulants (alkaloids)

- Nicotine
- Muscarine
- Pilocarpine

2. Anticholinesterase agents (agents that indirectly increase cholinergic function):

A. Reversible agents

- Physostigmine
- Neostigmine
- Edrophonium
- Pyridostigmine (Mestinon)
- Donepezil (Aricept)
- Tacrine (Cognex)

B. Irreversible agents

- Parathion & Malathion
- Sarin & Soman

3. Muscarinic blocking drugs:

- Atropine
- Scopolamine
- Tropicamide (Mydriacyl)
- Ipratropium (Atrovent)
- Benztropine (Cogentin)
- Oxybutynin

4. Ganglionic transmission:

A. Ganglionic stimulants

- Nicotine

B. Ganglionic blockade

- Hexamethonium

Introduction:

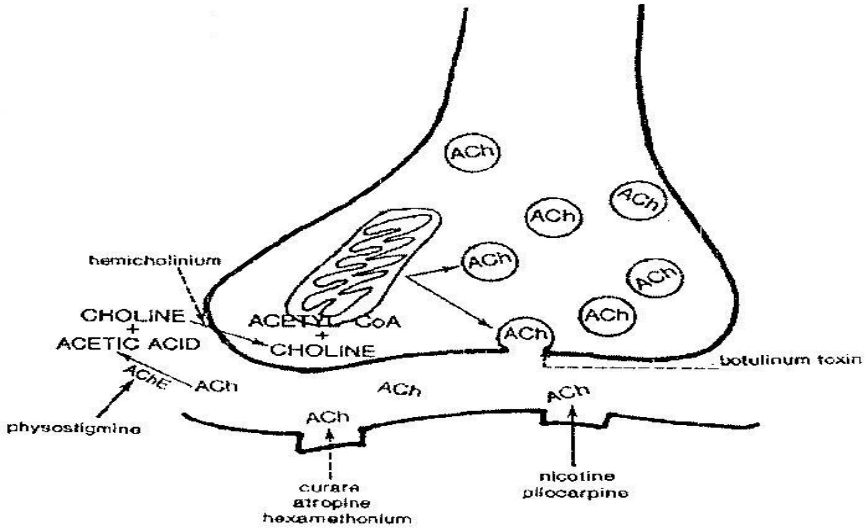
Cholinergic transmission:

All neurons in the peripheral or central nervous system that release acetylcholine (Ach) are referred to as cholinergic. Cholinergic synapses are found on a variety of structures including:

1. All parasympathetic neuroeffector junctions (smooth muscle, cardiac muscle & glandular tissue)
2. All autonomic ganglia (sympathetic & parasympathetic)
3. Skeletal neuromuscular junction
4. Sympathetic innervation of the adrenal medulla
5. Sweat glands (sympathetic-cholinergic)
6. Brain & spinal cord (CNS) sites

Many organs (particularly smooth muscle of blood vessels) also have non-innervated receptors for Ach on them. Non-innervated Ach receptors are generally of the muscarinic type. Thus, muscarinic stimulants will lower blood pressure when injected even through parasympathetic nerve stimulation cannot lower blood pressure.

Cholinergic drugs can either block or enhance cholinergic function in the body. Drugs that increase cholinergic function in the body. Drugs that increase cholinergic function can do this either directly by stimulating cholinergic receptors (e.g. nicotinic or muscarinic stimulants) or indirectly by increasing the effectiveness of endogenous Ach (e.g. anticholinesterase drugs). Drugs that decrease cholinergic function usually occupy the receptor so the Ach molecules cannot act on them (nicotinic or muscarinic blocking agents). Blockade of synthesis or release of Ach will also inhibit cholinergic function indirectly.



The Cholinergic Neuron:

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic & sympathetic), & the postganglionic fibers of the parasympathetic division use acetylcholine as a neurotransmitter. Cholinergic neurons innervate the muscles of the somatic system, & also play an important role in the central nervous system (CNS).

A. Neurotransmission at cholinergic neurons:

Neurotransmission in cholinergic neurons involves six steps. The first four synthesis, storage, release & binding of the acetylcholine to a receptor, are followed by the fifth step, degradation of the neurotransmitter in the synaptic gap, & the sixth step, the recycling of choline.

1. Synthesis of acetylcholine:

Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by a carrier system that cotransports sodium, & can be inhibited by the drug Hemicholinium. The uptake of choline is the rate limiting step in acetylcholine synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl CoA to form acetylcholine in the cytosol.

2. Storage of acetylcholine in vesicles:

The acetylcholine is packaged into vesicles by an active transport process coupled to the efflux of protons. The mature vesicle contains not only acetylcholine but also adenosine triphosphate (ATP) & proteoglycan. The function of the latter substances in the nerve terminal is not completely understood.

3. Release of acetylcholine:

When an action potential propagated by the action of voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels in the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane & release of their contents into the synaptic cleft. This release can be blocked by botulinum toxin.

4. Binding to the receptor:

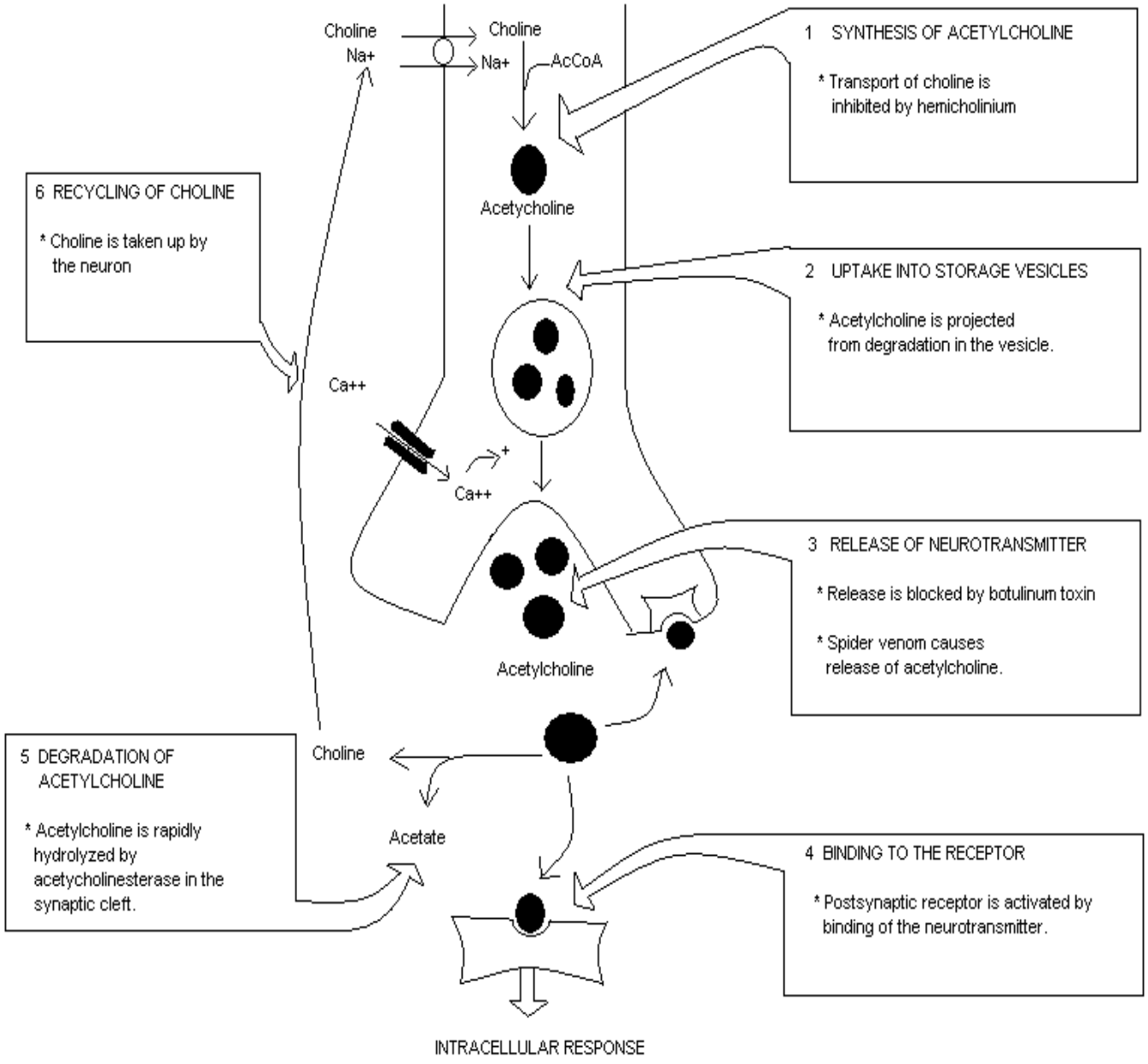
Acetylcholine released from the synaptic vesicles diffuses across the synaptic space, & binds to either of two postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the acetylcholine. Binding to a receptor leads to a biological response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells as mediated by second messenger molecules.

5. Degradation of acetylcholine:

The signal at the postjunctional effector site is rapidly terminated, because acetylcholinestrease cleaves acetycholine to choline & acetate in the synaptic cleft.

6. Recycling of choline:

Choline may be recaptured by a sodium coupled, high-affinity uptake system that transports the molecule back into the neuron, where it is acetylated & stored until released by a subsequent action potential.



Cholinergic receptors (Cholioceptors)

Two families of cholinoceptors, designated muscarinic & nicotinic receptors, can be distinguished from each other on the basis of selective effects of two agonists from plant material (alkaloids).

Muscarinic receptors:

Five subtypes of muscarinic receptors have been identified. M2 receptors are found in the heart. M3 receptors are located in peripheral autonomic organs & the others are found in the GI tract & autonomic ganglia (M1) & in the CNS (M1 to M5). Stimulation of muscarinic receptors will result in activation of a variety of peripheral autonomic organs.

Location of muscarinic receptors:

Heart:

Heart rate is slowed by stimulation of muscarinic receptors on atrial pacemaker cells. This is due to increase in K+ permeability that causes a prolongation of phase 4 depolarization. Muscarinic receptors produce little direct effect on force of ventricular contraction.

Vascular smooth muscle:

Although most blood vessels are not innervated by cholinergic nerves, systemic administration of Ach & other muscarinic stimulants produces a profound vasodilation & decrease of blood pressure. It is believed that Ach acts of non-innervated muscarinic receptors on endothelial cells of blood vessels that, in turn, release an endothelium derived relaxing factor (EDRF) to cause relaxation of the blood vessel smooth muscle. EDRF is nitric oxide (NO).

Eye:

The eye is innervated by parasympathetic nerves to the sphincter muscle of the iris & to the ciliary body controlling shape of the lens. Muscarinic agonists thus produce papillary constriction (miosis) & spasm of accommodation (cyclotonia).

Gastrointestinal tract:

Muscarinic agonists increase tone & motility of the GI tract from the lower esophagus to the rectum; only the smooth muscles of some sphincters appear to relax (the lower esophageal sphincter is stimulated). Bladder motility is similarly activated by muscarinic receptors (especially the detrusor muscle) although the bladder sphincters relax.

Bronchiolar smooth muscle:

Only a modest constriction is produced by muscarinic agonists in man. In asthmatic patients & in some experimental animals this effect is much greater.

Secretory glands:

Sweat glands are innervated by sympathetic nerves that paradoxically release Ach (sympathetic-cholinergic system). Thus, muscarinic receptor stimulation causes sweating. Lacrimal, salivary, bronchial & intestinal glands all possess muscarinic receptors that augment secretion.

CNS:

Many muscarinic cholinergic synapses are found in the cortex & brain stem although their precise functional significance remains undertermined.

Mechanisms of acetylcholine signal transduction:

A number of different molecular mechanisms transmit the signal generated by acetylcholine occupation of the receptor.
For example:

When M1 or M3 receptors are activated, the receptor undergoes a conformational change & interacts with a G protein, designated Gq, which in turn activates phospholipase C. This leads to the hydrolysis of phosphatidylinositol-(4-5)-biphosphate (P1P2) to yield diacylglycerol (DAG) & inositol (1,4,5)-triphosphate (IP3), which cause an increase in intracellular Ca++. This cation can then interact to stimulate or inhibit enzymes, or cause hyperpolarization, secretion, or contraction. In contrast activation of the M2 subtype on the cardiac muscle stimulates a G protein, designated Gi, that inhibits adenylyl cyclase, & increase K+ conductance, to which the heart responds with a decrease in rate & force of contraction.

Nicotinic Receptors:

Nicotine will activate Ach receptors at certain cholinergic synapses including:

NMJ:

All somatic nerves release Ach, which activates nicotinic receptors at the neuromuscular junction on the motor endplate of skeletal muscle.

Autonomic ganglia:

Both sympathetic & parasympathetic post-ganglionic neurons are stimulated by Ach acting on nicotinic receptors.

Adrenal medulla:

The synapse between the preganglionic sympathetic splanchnic nerve & chromaffin cells of adrenal gland is analogous to the ganglionic synapse. Ach produces release of epinephrine & Norepinephrine by excitation of nicotinic receptors.

CNS:

Some cholinergic synapses in the brain & many in the spinal cord are nicotinic.

Direct-acting cholinergic agonists:

Cholinergic agonists mimic the effects of acetylcholine by binding directly to cholinoceptors. These agents are synthetic esters of choline, such as Carbachol & bethanechol, naturally occurring alkaloids, such as Pilocarpine. All the direct-acting cholinergic drugs have longer durations of action than acetylcholine. Some of the more therapeutically useful drugs preferentially bind to muscarinic receptors, & are sometimes referred as to as muscarinic agents.

A. Acetylcholine:

Acetylcholine is a quarternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic & somatic nerves as well as ganglia, it is therapeutically of no importance because of its multiplicity of actions, & its rapid inactivation by the cholinesterases. Acetylcholine has both muscarinic & nicotinic activity. Its actions include:

1. Decease in heart rate & cardiac output:

The actions of acetylcholine on the heart mimic the effects of vegal stimulation.
For example, acetylcholine, if injected intravenously, produces a brief decrease in cardiac rate & stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node.

2. Decrease in blood pressure:

Injection of acetylcholine causes vasodilation & lowering of blood pressure. Although no innervation of the vasculature by the parasympathetic system exists, there are cholinergic receptors on the blood vessels that respond by causing vasodilation. The vasodilation is due to an acetylcholine-induced rise in the intracellular Ca++, caused by the phosphatidylinositol system that results in the formation of nitric oxide (NO) from arginine in endothelial cells.

3. Other actions:

Gastrointestinal tract

In the gastrointestinal tract, acetylcholine increases salivary secretion & stimulates intestinal secretions & motility. Bronchiolar secretions are also enhanced.

Genitourinary tract

In the genitourinary tract, the tone of the detrusor urinae muscle is increased.

Eye

In the eye, acetylcholine is involved in stimulating ciliary muscle contraction for near vision, & in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil).

B. Bethanechol:

Bethanechol is structurally related to acetylcholine, in which the acetate is replaced by carbamate & the choline methylated. Hence, it is not hydrolyzed by acetylcholinestrease, although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder & gastrointestinal tract. It has a duration of action of about one hour.

1. Actions:

Bethanechol directly stimulates muscarinic receptors, causing increased intestinal motility & tone. It also stimulates the detrusor muscles of the bladder while the trigone & sphincter are relaxed, causing expulsion of urine.

2. Therapeutic applications:

In urologic treatment, bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.

3. Adverse effects:

Bethanechol causes the effects of generalized cholinergic stimulation. These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea & bronchospasm.

C. Carbachol (carbamylcholine)

Carbachol has both muscarinic as well as nicotinic actions. Like bethanechol, carbachol is an ester of carbamic acid & a poor substrate for acetylcholinestrease. It is biotransformed by other esterases, but at a much slower rate. A single administration can last as long as one hour.

1. Actions:

Carbachol has profound effects on both the cardiovascular system & the gastrointestinal system because of its ganglion-stimulating activity, & it may first stimulate & then depress these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of acetylcholine, causing miosis & a spasm of accommodation.

2. Therapeutic uses:

Because of its high potency & relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing papillary contraction & a decrease in intraocular pressure.

3. Adverse effects:

At doses used ophthalmologically, little to no side effects occur.

D. Pilocarpine

The alkaloid pilocarpine is a tertiary amine, & is stable to hydrolysis by acetylcholinestrease. Compared with acetylcholine & its derivatives, it is far less potent. Pilocarpine exhibits muscarinic activity & is used primarily in ophthalmology.

1. Actions:

Applied topically to the cornea, pilocarpine produces a rapid miosis & contraction of the ciliary muscle. The eye undergoes miosis & a spasm of accommodation, the vision is fixed at some particular distance, making it impossible to focus. Pilocarpine is one of the most potent stimulators of secretions such as sweat, tears, & saliva, but its use for producing these effects has been limited due to its lack of selectivity.

2. Therapeutic use in glaucoma:

Pilocarpine is the drug of choice in the emergency lowering of intraocular pressure of both narrow angle (also called closed-angle) & wide-angle (also called open-angle) glaucoma.

3. Adverse effects:

Pilocarpine can enter the brain & cause CNS disturbances. It stimulates profuse sweating & salivation.

ANTICHOLINESTERASES (REVERSIBLE)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate & choline &, thus, terminates its actions. It is located both pre & postsynaptically in the nerve terminal, where it is membrane bound. Inhibitors of acetycholinesterase indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings.

A. Physostigmine:

Physostigmine is an alkaloid & a tertiary amine. It is a carbamic acid ester & a substrate for acetylcholinestrease, & it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

1. Actions:

Physostigmine has a wide range of effects as a result of its action, & not only the muscarinic & nicotinic sites of the autonomic nervous system but also the nicotinic receptors of the neuromuscular junction are stimulated. Its duration of action is about two to four hours. Physostigmine can enter & stimulate the cholinergic sites in the CNS.

2. Therapeutic uses:

The drug increases intestinal & bladder motility, which serve as its therapeutic action in atony of either organ. Placed topically in the eye, it produces miosis & spasm of accommodation, as well as a lowering of intraocular pressure. It is used to treat glaucoma, but pilocarpine is more effective.
Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, phenothiazines & tricyclic antidepressants.

3. Adverse effects:

The effects of physostigmine on the CNS may lead to convulsions when high doses are used. Bradycardia & a fall in cardiac output may also occur. Inhibition of acetylcholinesterase at the skeletal neuromuscular junction causes the accumulation of acetylcholine &, ultimately, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

B. Neostigmine

Neostigmine is a synthetic compound that is also a carbamic acid ester, & reversibly inhibits acetylcholinesterase in a manner similar to that of physostigmine. Its effect on skeletal muscle is greater than that of physostigmine, & it can stimulate contractility before it paralyzes.

It is used to stimulate the bladder & GI tract, & it is also used as an antidote for tubocurarine & other competitive neuromuscular blocking agents. Neostigmine has found use in symptomatic treatment of myasthenia gravis, (an autoimmune disease caused by antibodies to the nicotinic receptor at neuromuscular junctions).

Adverse effects:

Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea & bronchospasm.

C. Pyridostigmine:

Pyridostigmine is other cholinesterase inhibitor that is used in the chronic management of myasthenia gravis. Their durations of action are longer than that of neostigmine, but their adverse effects are similar.

D. Edrophonium:

The actions of edrophonium are similar to those of neostigmine, except that it is more rapidly absorbed & has a short duration of action. Edrophonium is a quarternary amine & is used in the diagnosis of myasthenia gravis. Intravenous injection of edrophonium leads to a rapid increase in muscle strength.

E. Donepezil & Tacrine:

Donepezil & Tacrine are CNS acting anticholinesterase drugs used to treat cognitive dysfunction seen in patients with Alzheimer’s disease.

ANTICHOLINESTERASES (IRREVERSIBLE)

These phosphorous containing compounds phosphorylate the esteratic site on the ACHASE enzyme. As they so strongly bind to the enzyme, recovery depends upon regeneration of the enzyme. Organophosphate anticholinesterases thus have prolonged & pronounced effects on cholinergic systems. Although several of these compounds are used topically to treat glaucoma, most are insecticides & are potent war gases. These agents are lipid soluble & absorbed through the skin. The major medical consideration with these compounds is toxicological.

Parathion & Malathion:

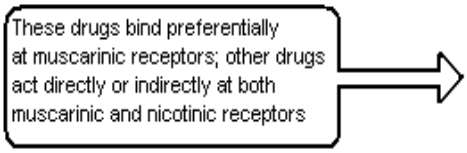
Parathion & Malathion are common insecticides used in agriculture. Parathion itself is not an antiAChase compound but is converted by the liver to the active agent paraoxon. Malathion is quickly inactivated to non-toxic metabolites in mammals & birds.

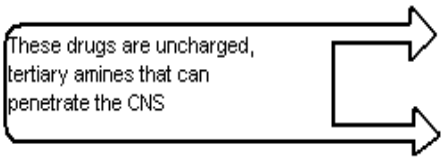
Sarin & Soman:

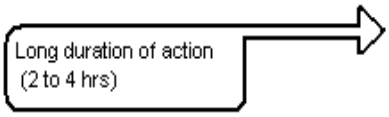
Sarin & Soman are potent anti-cholinesterase war gases. Unfortunately, their actions are not reversed by the enzyme reactivators.

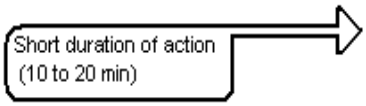
Isoflurophate:

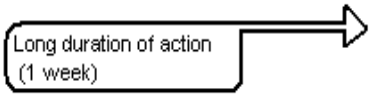
Isoflurophate actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), & convulsions. Isoflurophate produces intense miosis &, thus, has found therapeutic use. It is used in ophthalmic ointment of the drug is used topically in the eye for the chronic treatment of open-angle glaucoma.











Drug	Therapeutic uses
Acetylcholine	None
Bethanechol	Treatment of urinary retention
Carbachol	Miosis during ocular surgery
Pilocarpine	Reduce intraocular pressure in open-angle and narrow-angle glaucoma
Physostigmine	Increase intestinal and bladder motility
	Reduce intraocular pressure in glaucoma
	Reverse CNS and cardiac effects of tricyclic antidepressants
	Reverse CNS effects of atropine
Neostigmine	Prevent postoperative abdominal distention and urinary retention
	Treat myasthenia gravis
	As antidote for tubocurarine
Edrophonium	For diagnosis of myasthenia gravis
	As antidote for tubocurarine
Isoflurophate	Treatment of open angle-glaucoma

Summary of actions of some cholinergic agonists

CHOLINERGIC ANTAGONISTS 5

The cholinergic antagonists bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects.

ANTIMUSCARINIC AGENTS

These agents block muscarinic receptors, causing inhibition of all muscarinic functions.

A. Atropine

Atropine, a belladonna alkaloid, has a high affinity for muscarinic receptors, where it binds competitively, and preventing acetylcholine from binding to those sites. Atropine acts both centrally & peripherally. Its general actions last about four hours except when placed topically in the eye, where the action may last for days.

1. Actions:

a. Eye:

Atropine blocks all cholinergic activity on the eye, resulting in persistent mydriasis, unresponsiveness to light, & cycloplegia (inability to focus for near vision).

b. Gastrointestinal (GI):

Atropine can be used as an antispasmodic to reduce activity of the GI tract. Although GI motility is reduced, hydrochloric acid production is not significantly affected.

c. Urinary System:

Atropine is also employed to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children, but α-adrenergic agonists with fewer side effects may be more effective.

d. Cardiovascular:

Atropine produces divergent effect on the cardiovascular system, depending on the dose. At low doses, the predominant effect is a decreased cardiac rate (bradycardia).

e. Secretion:

Atropine blocks the salivary glands, producing a drying effect on the oral mucus membranes. The salivary glands are exquisitely sensitive to atropine. Sweat & lacrimal glands are also affected.

2. Therapeutic uses:

a. Ophthalmic:

In the eye, topical atropine exerts both mydriatic & cycloplegic effects, & it permits the measurement of refractive errors without interference by the accommodative capacity of the eye.

b. Antispasmodic agent:

Atropine is used as an antispasmodic agent to relax the GI tract & bladder.

c. Antidote for cholinergic agonists:

Atropine is used for the treatment of overdoses of cholinesterase inhibitor insecticides & some types of mushroom poisoning.

d. Antisecretory agent:

The drug is sometimes used as an antisecretory agent to block secretions in the upper & lower respiratory tracts prior to surgery.

3. Adverse effects:

Depending on the dose, atropine may cause dry mouth, blurred vision, “sandy eyes”, tachycardia, and constipation.

B. Scopolamine

Scopolamine, another belladonna alkaloid, produces peripheral effects similar to those of atropine. However, scopolamine has greater action on the CNS & a longer duration of action in comparison to those of atropine. It has some special actions as indicated below.

1. Actions:

   Scopolamine is one of the most effective anti-motion sickness drugs available. Scopolamine also has the unusual effect of blocking short-term memory.

2. Therapeutic uses:

   It prevent motion sickness & to block short-term memory.

3. Pharmacokinetics & adverse effects:

   These aspects are similar to those of atropine.

C. Ipratropium

Inhaled ipratropium is useful in treating asthma in patients who are unable to take adrenergic agonists.

GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic & sympathetic autonomic ganglia.

A. Nicotine

A component of cigarette smoke, nicotine has many undesirable actions. Depending on the dose, nicotine depolarizes ganglia, resulting first in stimulation & then paralysis of all ganglia. The stimulatory effects are complex, including increased blood pressure & cardiac rate & increase peristalsis & secretions.

B. Trimethaphan

Trimethaphan is a short-acting, competitive nicotinic ganglionic blocker that must be given by intravenous infusion. This drug is used for the emergency lowering of blood pressure.

C. Mecamylamine

Mecamylamine produces a competitive nicotinic blockade of the ganglia. The duration of action is about ten hours after a single administration. The uptake of the drug via oral absorption is good in contrast to that of trimethaphan.

	Drug	Therapeutic uses
Muscarinic Blockers	Atropine	In ophthalmology, to produce mydriasis and cycloplegia prior to refraction To treat spastic disorders of the GI and lower urinary tract To treat organophosphate poisoning To supress respiratory secretions prior to surgery
	Scopolamine	In obstetrics, with morphine to produce amnesia and sedation To prevent motion sickness
	Ipratopium	Treatment of asthma
Ganglionic Blockers	Nicotine	None
	Trimethaphan	Short-term treatment of hypertension
	Mecamylamine	Treatment of moderately severe to severe hypertension

Summary of cholinergic antagonists

ADRENERGIC PHARMACOLOGY 6

The adrenergic drugs affect receptors that are stimulated by nor-epinephrine or epinephrine. Some adrenergic drugs act directly on the adrenergic receptor by activating it, & are said to be sympathomimetic.

THE ADRENERGIC NEURON

Adrenergic neurons release Norepinephrine as the neurotransmitter. These neurons are found in the central nervous system (CNS) & also in the sympathetic nervous system, where they serve as links between ganglia & the effector organs. The adrenergic neurons & receptors, located either presynaptically on the neuron or postsynaptically on the neuron or postsynaptically on the effector organ, are the sites of action of the adrenergic drugs.

A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that already described for the cholinergic neurons, except that Norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission takes place at numerous bead-like enlargements called varicosities.

The process involves five steps:

1. Synthesis
2. Storage
3. Release
4. Receptor binding of the Norepinephrine
5. Removal of neurotransmitter

1. Synthesis of Norepinephrine:

Tyrosine is transported by a Na+ linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to the dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated to form dopamine.

2. Storage of norepinephrine in vesicles:

Dopamine is transported into synaptic vesicles by an amine transporter system that is also involved in the re-uptake of preformed Norepinephrine. This carrier system is blocked by reserpine. Dopamine is hydroxylated to form Norepinephrine by the enzyme, dopamine β-hydroxylase. In the adrenal medulla, Norepinephrine is the methylated to yield epinephrine, both of which are stored in chromaffin cells. On stimulation, the adrenal medulla releasesabout 85 % epinephrine & 15 % Norepinephrine.

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 vesicles inside the neuron to fuse with the cell membrane & expel their contents into the synapse. This release is blocked by drugs such as guanethidine.

4. Binding to a receptor:

Norepinephrine released from the synaptic vesicles diffuses across the synaptic space & binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. The recognition of norepinephrine by the membrane 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 & the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system & the phosphatidylinositol cycle to transducer the signal into an effect.

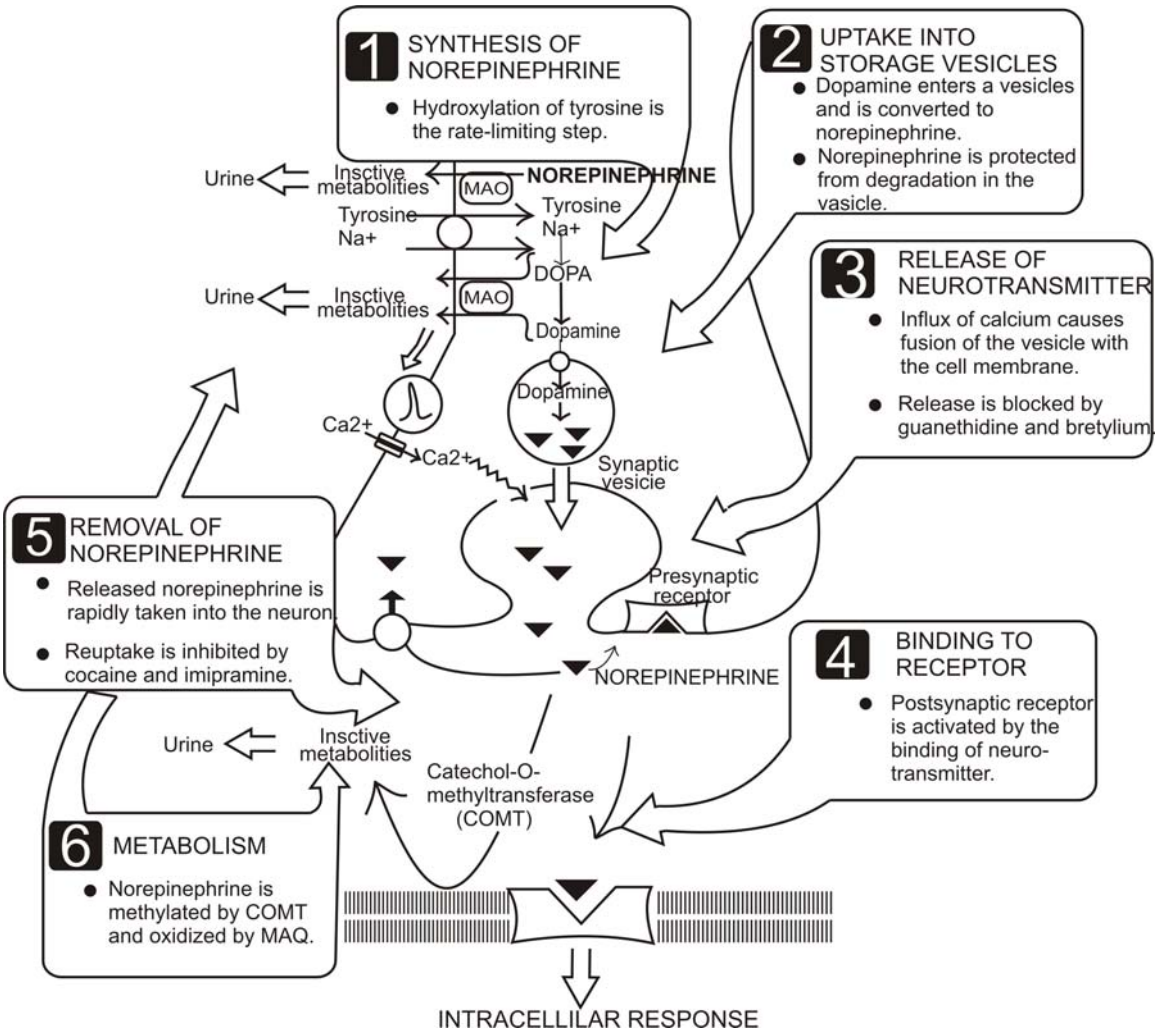
5. Removal of norepinephrine:

Norepinephrine may

1. Diffuse out of the synaptic space & enter the general circulation
2. Metabolized to O-methylated derivatives by postsynaptic cell membrane-associated catechol O-methyltransferase (COMT) in the synaptic space
3. Recaptured by an uptake system that pumps the norepinephrine back into the neuron. The uptake by the neuronal membrane involves a sodium/potassium-activated ATPase that can be inhibited by tricyclic antidepressants, such as imipramine, or by cocaine.

6. Potential fates of recaptured norepinephrine:

Once norepinephrine reenters the cytoplasm of the adrenergic neuron, it may be taken up into adrenergic vesicles via the amine transporter system & be sequestered for release by another action potential, or it may persist in a protected pool. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO), present in neuronal mitochondria. The inactive products of norepinephrine metabolism are excreted in the urine as vanillylmandelic acid, metanephrine, & normetanephrine.



B. Adrenergic receptors (adrenoceptors)

Noradrenergic neurons are regulated by several receptors, mainly α1, α2 & β1, β2, β3 with further subreceptors.

α (alpha) receptors	α1: located post-synaptically α2: located pre-synaptically
β (beta) receptors:	β1: located post-synaptically β2: located pre & post synaptically β3: located pre-synaptically

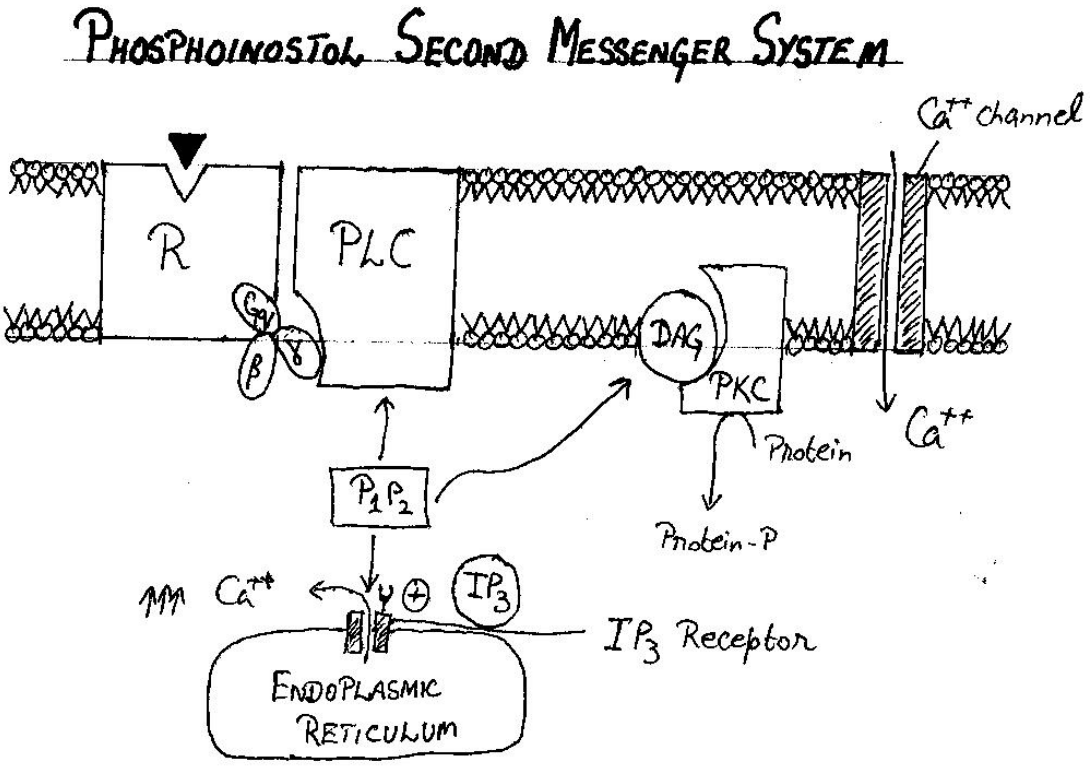
Activation of these receptors through the administration of adrenergic agonists will produce effects consistent with sympathetic flight or fight stimulation.

Activation of α1-adrenergic responses:

Stimulation of α1-adrenergic receptors by norepinephrine leads to the activation of a Gq coupling protein. The α subunit of this G protein activates the effector, phospholipase C, which leads to the release of IP3 & DAG from phosphatidylinositol 4, 5-biphosphate (PtdIns 4,5-P2). IP3 stimulates the release of sequestered stores of calcium, leading to an increased concentration of cytoplasmic Ca++. Ca++ may then activate Ca++ dependent protein kinases, which in turn phosphorylate their substrates. DAG activates protein kinase C.

Postsynaptic Alpha 1 & Alpha 2 Receptors: (IP3, DAG)

1. Phospholipase C (PLC) is a membrane bound enzyme that converts phosphatidyl inositol (1-4) biphosphate (P1P2) into Inositol (1,4,5) triphosphate (IP3) & diacylglycerol (DAG).
2. PLC is activated when a receptor complex activates a G-protein of Gq family.
3. The IP3 from as a plasma membrane binds to IP3 receptor on the endoplasmic membrane & release intracellular Ca++ store.
4. DAG remain membrane associated. PKC translocate from the cytosol to the membrane & becomes activated by that. Activated PKC, in term phosphorylate other proteins & alter their function state.
5. Activation of PLC system also causes the efflux of Ca++.
6. Ca++ for both extracellular & squestor intracellular sources binds one of the family of Ca++ binding proteins. This complex binds to yet other proteins & changes their functional activity.



α1- adrenergic receptors cause contraction of smooth muscle in the following organs:

- Eye: iris dilator muscle contraction (mydriasis-dilation)
- Arterioles: skin, cerebral, abdominal, & salivary gland
- Stomach & Intestine: contraction of sphincters
- Glandular Secretion: Lacrimal (increase), salivary (increase), bronchial (decrease), pancreatic (decrease), mucosal (decrease), & sweat (palms sympathetic increase)
- Pilomotor neck: sphincter contraction
- Sex Organs, Male: ejaculation
- Sex Organs, Female: if pregnant uterus contraction.

Inhibition of adenylyl cyclase by agonists that bind to α2-adrenergic receptors:

α2 adrenoceptor ligands inhibit adenylyl cyclase by causing dissociation of the inhibitory G protien, Gi, into its subunits; i.e. an α subunit charged with GTP & a beta-gamma unit. The mechanism by which these subunits inhibit adenylyl cyclase is uncertain.

α2-adrenergic receptors cause specific actions in the following organs:

- Arterioles: decreased release & synthesis of catecholamines.
- Stomach & Intestine: decrease motility
- Pancreas: decreased release of insulin
- Brain (cardiovascular control center): activation of α2-receptors by NE causes increased parasympathetic outflow & decreased sympathetic outflow.

Pharmacology of α1 receptors:

α1 receptors location	α1 receptors stimulation effects
• Vasoconstriction of blood vessels.	Effect on tissue perfusion. Redirect blood flow ▪ From one tissue to another. In many vessels this ▪ Stimulation provides resting vasomotor tone. ▪ Vasoconstriction of major systemic blood vessels results in elevation of blood pressure. ▪ Vasoconstriction is an effective mean to decongest nasal passages (nasal decongestants). ▪ Vasoconstriction of scleral blood vessels can greatly diminish the condition characterized by red eyes (ophthalmic decongestants).
• Radial muscle of the iris	Contraction of the radial muscle of the iris result in pupil dilation (mydriasis).
Sphincters & smooth muscle Of the gastro-intestinal tract	Contraction of gastrointestinal sphincters & decreased gastrointestinal motility resulting in slow in digestion & transport through the gut.

Sphincter	Contraction of the external sphincter & loss of bladder tone leading to urinary retention.
Bile	Decreased bile secretion & increased glycogenolysis. The latter leads to increased blood sugar levels.
Smooth muscle of the Vas-deferens & the non-Pregnant uterus	Contraction of the smooth muscle of the vas deferens & the non-pregnant uterus to facilitate emission & ejaculation in the former & sperm transport to the fallopian tubes in the latter.
Sweat glands	Stimulation off sweat glands resulting in general sweating.
Piloerector muscles	Contraction of the piloerector muscles Resulting in goose-flesh

Pharmacology of α2 receptors:

The α2 adrenergic receptors are located pre-synaptically & found on all adrenergic nerve terminals. They provide a local negative feedback control. When adrenergic stimulation is excessive & leads to a built-up of transmitter in the synapse, activation of α2 receptor results in inhibition of transmitter release from the terminal. This prevents over stimulation of the effector. The α2 receptors are located post-synaptically on some effectors, such as the pancreas.

Clinical applications α1 stimulation:

Direct acting α1 agonists:

- Methoxamine
- Naphazoline
- Oxymethazoline
- Phenyllephrine
- Xylomethazoline

Non-selective sympathomimetics:

- Noradrenaline
- Pseudoephedrine
- Metaraminol
- Adrenaline
- Ephedrine
- Dopamine

(These act on both α & β receptors)

Clinical Use of α1 stimulation:

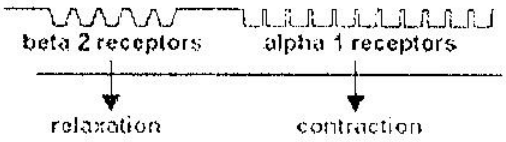
1. Control of hypotension
2. Nasal congestion
3. Red eyes
4. Used as vasoconstrictor administered in combination with another drug.

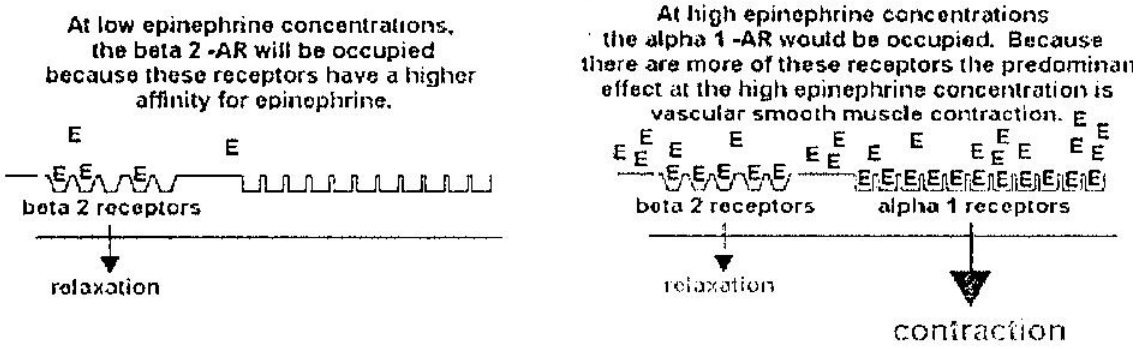
Clinical applications of α2 stimulation:

Clonidine & its derivative Apraclonidine are selective α2 agonists. They block sympathetic nerve transmission associated with vasomotor tone. Clonidine is used in the treatment of hypertension. It acts centrally at the level of the medulla. Apraclonidine is used as an adjunct in controlling glaucoma. It is applied topically & affects the rate of aqueous humor production.

Effect of Catecholamines on Vascular Smooth Muscle:

Associated with vascular smooth muscle are a large number of alpha1 receptors relative to beta2 receptors. However, epinephrine has a higher affinity for the beta2 receptors when compared to the alpha1 receptors. Therefore, the effect of epinephrine is dependent on which type of receptor is occupied. As we know that receptor occupancy is dependent on the concentration of a drug & its equilibrium dissociation constant.
At low doses epinephrine can selectively stimulate beta2 receptors, thus producing muscle relaxation & a decrease in peripheral resistance.
At high doses, epinephrine produces contraction of vascular smooth muscle & an associated increase in peripheral resistance.





Norepinephrine has little affinity for beta2 receptors. Therefore, it will stimulate only alpha1 receptors, producing an increase in peripheral vascular resistance. In contrast, Isoproterenol will only produce vasodilation due to activation of the beta2 receptors.

Pharmacology of β1 receptors:

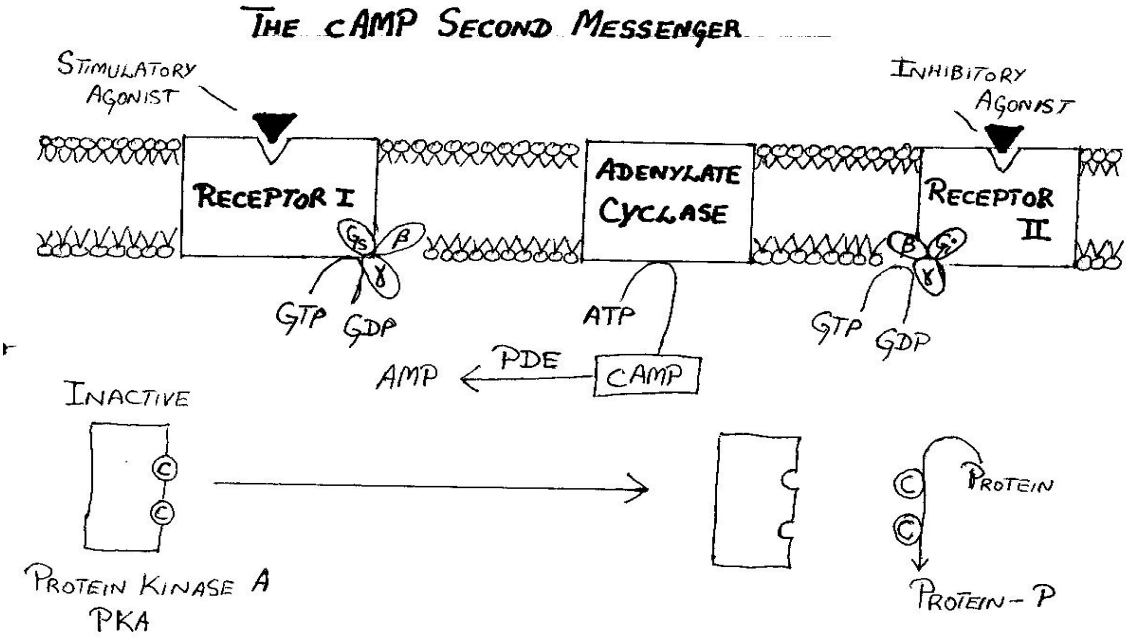
β1 are located on the myocardium, adipocytes, sphincters & smooth muscle of the gastrointestinal tract & renal arterioles. Stimulation of these receptors results in:

- Increased rate & force of contraction of the heart. The increased cardiac output can lead to an elevation of blood pressure.
- Decreased digestion & gastrointestinal motility.
- Release of rennin in to the renal blood, which causes an increase of renal blood flow & pressure, & as a result, increased glomerular filtration.

Tissue	Receptor Subtype
Heart	Beta 1
Adipose tissue	Beta 1, Beta 3
Vascular Smooth Muscle	Beta 2
Airway Smooth Muscle	Beta

Mechanism of Beta Receptor Activation:

1. cAMP is made by a family of membrane spannic enzyme collectively called Adenylate cyclase.
2. Receptors which associated with G-protein of Gs type stimulates adenylate cyclase. Receptors which associate with G-protein of Gi type inhibit adenylate cyclase.
3. The cAMP that is formed activates "cAMP dependent protein Kinase A" also called "Protein Kinase A" or "PKA".
4. The PKA phosphorylate other proteins (Enzymes, transporters etc) & depending on the protein increases or decreases that protein activity.



Pharmacology of β2 receptors:

β2 are distributed on the smooth muscle of the bronchioles, skeletal muscle, blood vessels supplying the brain, kidney, mast cells, the uterus, & liver cells. Stimulation of these receptors results in:

- Bronchodilation
- Increase skeletal muscle excitability resulting in fine muscle tremors.
- Vasodilation of blood vessels in the brain, heart, kidneys & skeletal muscle leading to increased blood flow through those tissues.

- Relaxation of the pregnant uterus & rhythmic contraction of the non-pregnant uterus during sexual intercourse to promote sperm transport towards the fallopian tubes.
- Decrease bile secretion & increased glycogenolysis.
- Stabilisation of the membrane of the mast cell preventing the release of inflammatory mediator.

β2 recptors are also located on the presynaptic terminal of adrenergic nerves & act to enhance the release of stored noradrenaline. They provide a positive feedback control.

β1-adrenergic receptors cause actions in the heart in the following manner:

Heart SA node: Increase in heart rate.
Heart AV node: Increase in automaticity & conduction velocity.
Heart Atria & Ventricles: Increase in contractility & conduction velocity

β2-adrenergic receptors cause relaxation or dilation of smooth muscle in the following organs:

Eye: Ciliary muscle relaxation (mydriasis-dilation)
Eye: Ciliary epithelium (β2 mediated increased aqueous humor production).
(Stimulation of α2 receptors, also found in ciliary epithelium, cause decrease in aqueous humor production).

Arterioles: (Coronary, skeletal muscle, pulmonary, abdominal & renal) dilation
Lungs: Tracheal & bronchial smooth muscle dilation
Stomach & Intestine: Decrease motility
Bladder: Detrusor muscle relaxation
Sex organs (Female): Relaxation

Clinical application of β1 stimulation:

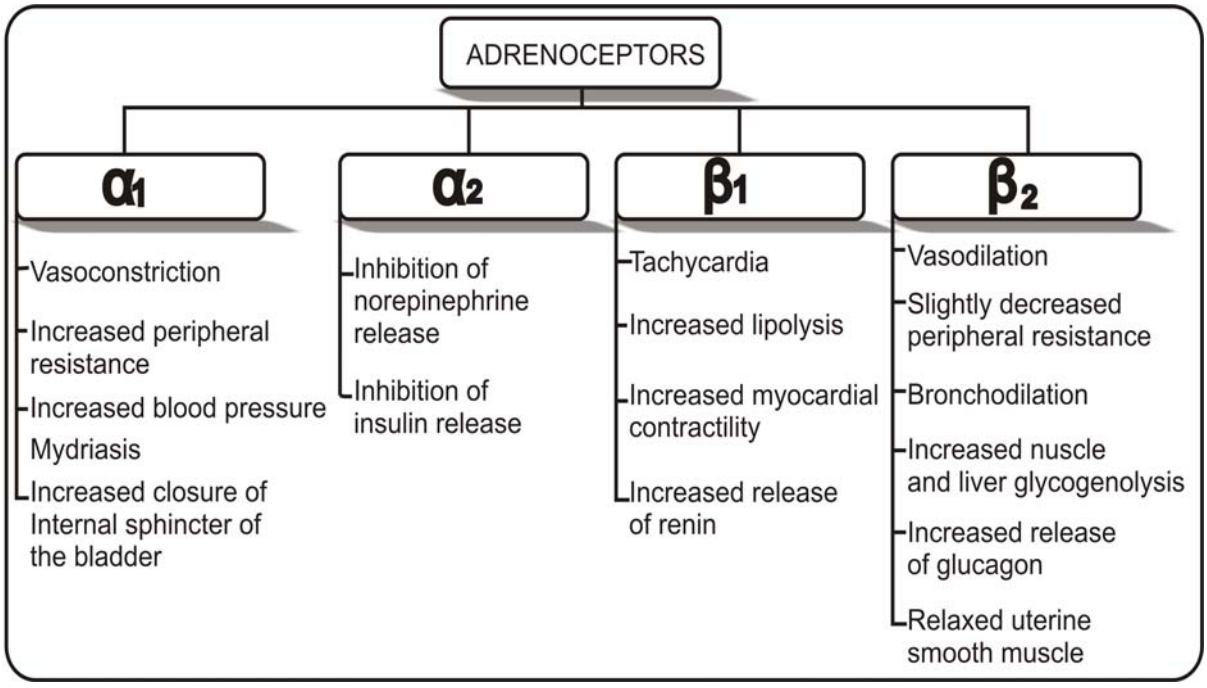
β1 stimulation is applied as positive inotrophic agents in circulatory shock, hypotension & cardiac arrest.
Dobutamine is a β1 agonist
Xameterol a β1 partial agonist
Isoprenaline is a β1 non-selective sympathomimetic agent.

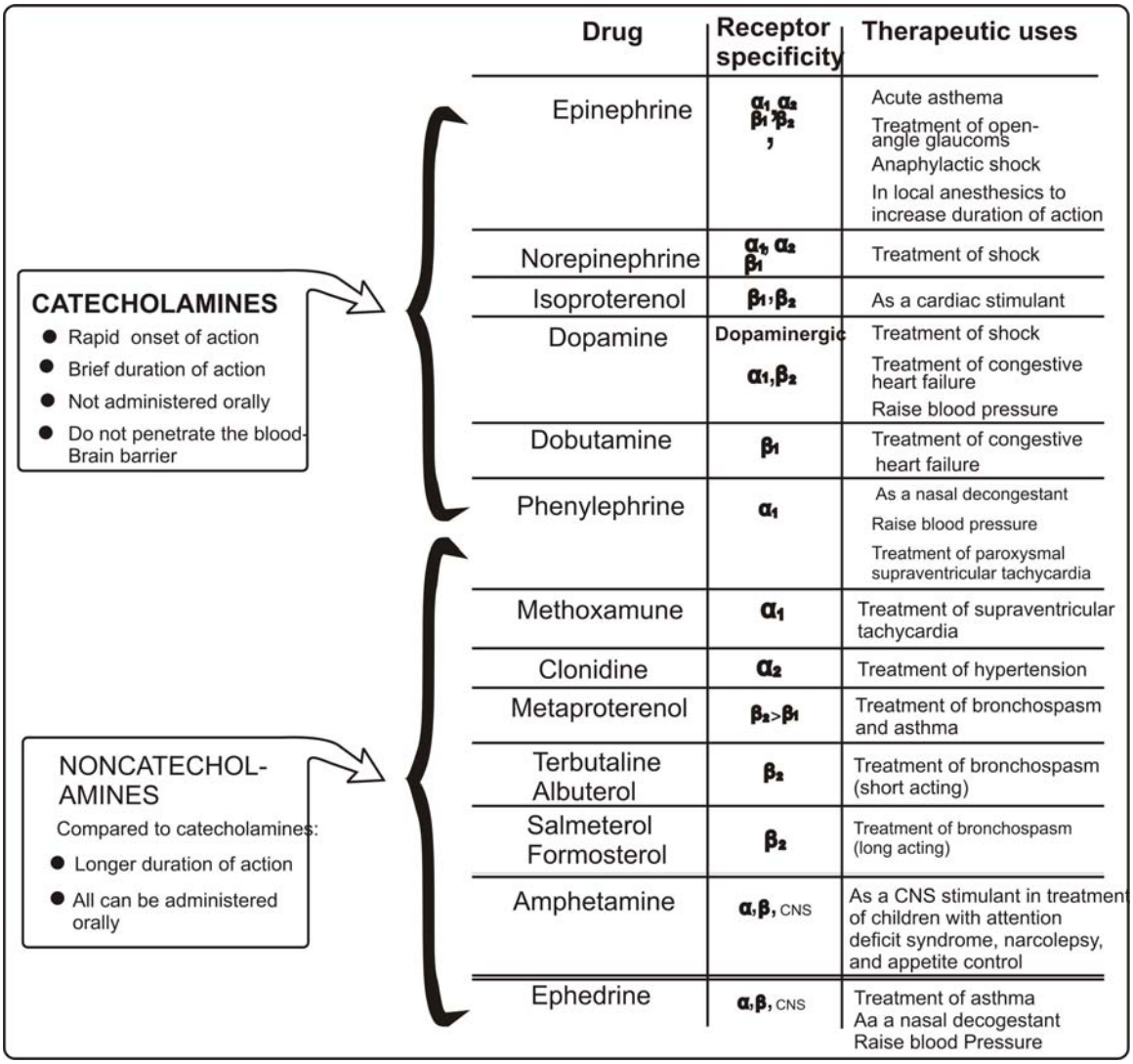
Clinical applications of β2 stimulation:

β2 stimulation is applied for chronic obstructive airways disease, circulatory shock, premature labour & peripheral vascular disease.
Fenotrol, Eformoterol, Hexoprenaline, Orciprenaline, Reproterol, Rimiterol, Salbutamol, Salmeterol, Terbutaline, Tolobuterol are relatively selective β2 agonists

Side effects of adrenergic drugs:

The adrenergic receptors are widely distributed around the body, therefore the administration of many adrenergic compounds can result in side-effects. For instance if an adrenergic drug has affinity for β receptors, effects will be observed in all effectors around the body bearing these receptors: Heart, bronchioles, adipose tissue, renal arterioles, brain & blood vessels to brain, heart & skeletal muscle etc.





Drug	Receptor specificity	Therapeutic uses
Epinephrine	α_1, α_2 β_1, β_2	Acute asthema Treatment of open-angle glaucoms Anaphylactic shock In local anesthesics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_2	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of congestive heart failure
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Methoxamune	α_1	Treatment of supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Metaproterenol	$\beta_2 > \beta_1$	Treatment of bronchospasm and asthma
Terbutaline Albuterol	β_2	Treatment of bronchospasm (short acting)
Salmeterol Formosterol	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and appetite control
Ephedrine	α, β, CNS	Treatment of asthma Aa a nasal decogestant Raise blood Pressure

Study Questions

Choose the one best answer.

1. A 68 years old man presents to the emergency department with acute heart failure. You decide that this patient requires immediate drug therapy to improve his cardiac function. Which one of the following drugs would be most beneficial?

A. Albuterol
B. Dobutamine
C. Epinephrine
D. Norepinephrine

Correct Answer = B

Dobutamine increases cardiac output without significantly increasing heart rate—a complicating condition in heart failure. Because epinephrine can significantly increase heart rate, it is not usually employed for acute heart failure.

2. Remedies for nasal stuffiness often contain which one of the following drugs?

A. Albuterol
B. Atropine
C. Phenylephrine
D. Epinephrine

Correct Answer = C

Phenylephrine is an α agonist that constricts the nasal mucosa, thereby decreasing airway resistance.

Adrenergic Antagonists 7

Adrenergic Receptor Antagonists
(sympatholytic Drugs)

Defination: Drugs that decreases sympathetic neuronal activity
Classification according to mechanism of action:

1. Indirect-acting:
   - Drugs that interfere with sympathetic neuronal function by inhibiting:

   (a) Synthesis of NE
   (b) Storage of NE
   (c) Release of NE

   (Used mainly to treat hypertension)

2. Direct-acting:

   - Adrenergic Receptor Antagonists:
     Drugs that bind to adrenergic receptors but don't activate them

   It includes:

   a) α receptor blocking drugs: Treatment of hypertension (limited use)
   b) β receptor blocking drugs: Treatment of cardiovascular disorders (widely used)

      - Nonselective: Block both β1 & β2 receptors
      - Selective: Block either β1 & β2 receptors

1. Drugs that interfere with Sympathetic Neuronal Function

i) Inhibit synthesis of NE

a) Metyrosine

- Inhibits tyrosine hydroxylase
- Decreased dopamine NE & EP
- Used in patients with pheochromocytoma (tumor of the adrenal gland which secretes NE & EP)
- Signs of catecholamine excess e.g. Hypertension, tachycardia & arrhythmias

b) Carbidopa

- Acts like methyldopa & blocks peripheral dopa decarboxylase activity
- Decreased formation of dopamine (no effect on NE)
- Doesn't cross blood-brain barrier (acts only peripherally)
- Decreased side effects (motor symptoms) due to dopamine formation in peripheral tissues of patients with Parkinson's disease treated with L-dopa

ii) Prevents storage

c) Reserpine

- Decrease storage of NE which leaks from vesicles & is deaminated by MAO
- Effects are decreased peripheral resistance
- Used in low doses with diuretics to treat mild hypertension
- Long duration of action
- Not widely used

iii) Inhibit release

d) Guanethidine

- Impairs the release of norepinephrine from presynaptic sympathetic neurons
- Doesn't cross blood-brain barrier
- Taken up by nerve terminals & stored in synaptic vesicles
- Decreases release of NE in response to action potentials or indirect acting sympathomimetics
- Decreases response of α & β receptors equally
- Decrease sympathetic tone to all organs

Side effects:

- Decreased BP, HR & CO & postural hypotension
- Increased gut motility & diarrhea
- Nasal stuffiness, impaired ejaculation

Use:

Because of side effects, only used for moderate to severe hypertension.

e) Bretylium

- Accumulates in noradrenergic sympathetic neurons
- Decrease release of NE
- Direct & indirect effects on the heart
- Used for treatment of ventricular dysrhythmias

iv) Reduction of central sympathetic flow

f) Methyldopa

- Drugs that decrease sympathetic outflow in the CNS. Both activate α2 receptors in the hypothalamus & medulla
- Decrease sympathetic outflow
- Decreased total peripheral resistance, HR, CO
- Decrease BP
- No postural hypotension because they don't interfere with baroreceptor reflexes.

1) α Receptor Blocking Drugs

Types of α blockers:

- Nonselective: e.g. Phenoxybenzamine & Phentolamine (α1 & α2)
- Selective: e.g. Prazosin (α1)

Clinical Pharmacology:

Mechanism:

- α receptors are present on vascular smooth muscle
- Control arteriolar & venous tone
- α1 blockade (Vasodilation, decreased peripheral resistance & BP)

Reflex sympathetic control of capacitance vessels is blocked (Postural hypotension "A fall in blood pressure associated with dizziness, syncope & blurred vision occurring upon standing." & reflex tachycardia)

- α2 blockade enhances this reflex tachycardia because the inhibitory effect on NE release is blocked.
- More NE released to stimulate β1 receptors in the heart

Major side effects of α blockers:

- Postural hypotension
- Reflex tachycardia
- Inhibition of ejaculation
- Nasal stuffiness

A) Nonselective α blockers:

i) Phenoxybenzamine (Dibenzyline)

- Irreversible α1 & 2 receptors blockade
- Binds covalently to receptor (14-28 hours duration)
- Blocks catecholamine-induced vasoconstriction
- Used to diagnose & treat pheochromocytoma (tumor of adrenal gland which secretes NE & EP)
- Signs of catecholamine excess e.g. hypertension, tachycardia & arrhythmias
- Also used to correct severe hypertension & decrease blood volume before patient with pheochromocytoma undergoes surgery
- Causes postural hypotension, tachycardia
- Also acts centrally to cause nausea, vomiting, sedation & weakness

ii) Phentolamine (Regitine)

- Potent competitive reversible α 1 & 2 receptor blocker
- Major clinical use in treatment of pheochromocytoma
- Used to treat episodes that occur during surgical removal of tumor

- Causes postural hypotension, tachycardia
- Also stimulates gastrointestinal tract
- Abdominal pain & diarrhea (not α blocking effect)

B) Selective α blockers:

i) Prazosin (Minipress)

- Potent selective α1 receptor antagonist (reversible)
- Causes dilation of both arterial & venous smooth muscle
- Effective in the management of chronic hypertension
- Well absorbed orally but substantial first pass metabolism only 50% available
- Causes less tachycardia because α2 receptors aren't blocked

2) β Receptor Blocking Drugs

(Drugs that antagonize the effects of catecholamines at β receptors)

General characteristics of β blockers:

- All are pure antagonists (i.e. no receptor activation)
- Those with higher affinity for β1 & β2 are important clinically
- Most resemble Isoproterenol (β receptor agonist)
- Most are well absorbed but low bioavailability due to extensive hepatic metabolism
- Variable plasma concentration due to individual variations in metabolism
- e.g. decreased elimination in
- Liver disease
- Decreased blood flow to liver
- Inhibition of liver enzymes

Effects & Clinical Uses:

- Predictable from blockade of β adrenergic receptors
- Important cardiovascular & ophthalmic applications

a) Propranolol

- Prototype β blocking drug
- Potent reversible β1 & β2 receptor antagonist
- Blocks positive chronotropic & inotropic effects on heart
- Effects more dramatic during exercise

Clinical Use:

Various cardiovascular diseases (i.e.hypertension, angina, dysrhythmia, postmyocardial infarction etc.)

Side Effects:

- Few in normal individuals, can occur in disease states
- Predictable from β blockade

i) Patient with diabetes:

- Propranolol blocks metabolic effects of β receptor stimulation (i.e. inhibits increase in free fatty acids & glycogenolysis)
- Can increase insulin-induced hypoglycemia

ii) Patients with heart disease:

- Contraindicated in patients with sinus bradycardia, partial heart block & congestive heart failure
- CO depends on sympathetic output which is decreased with β blockers
- Withdrawal symptoms (i.e. angina, tachycardia, dysrhythmias) may develop after withdrawal from long term patients

iii) Patients with asthma:

- β2 receptor blockade can increase airway resistance
- Selective β1 blockers should be used

b) Timolol

- Nonselective β adrenergic blocker used orally for hypertension & angina, & not topically for the treatment of glaucoma

c) Selective β1 adrenergic blockers (acebutolol, metoprolol, esmolol)

- Less likely to increase bronchoconstriction in patients with asthma
- Useful in the treatment of hypertension & angina pectoris

Clinical Pharmacology of β blockers

Used in the treatment of

a) Hypertension:

- Decreased BP mainly due to effects on the heart i.e. negative inotropic & chronotropic effects

b) Ischemic heart disease: (e.g. angina)

- Decreased angina & increased exercise tolerance due to decreased cardiac work, decreased HR, & decreased oxygen demand

c) Cardiac arrhythmias:

β1 blockade results in:

- Decreased rate of spontaneous discharge of SA node
- Decreased AV conduction
- Decreased AV node refractory period
- Decreased ventricular response to atrial flutter
- Decreased ventricular or ectopic beats

Study Questions

Choose the one best answer.

1. A 38 years old male has recently started monotherapy for mild hypertension. At his most recent office visit, he complains of tiredness and not being able to complete three sets of tennis. Which one of the following drugs is he likely to be taking for hypertension?

A. Albuterol
B. Atenolol
C. Ephedrine
D. Prazosin

Correct Answer = B

Atenolol is a β1 antagonist, and is effective in lowering blood pressure in patients with hypertension. Side effects of β-blockers include fatigue and exercise intolerance.

2. A 60 years old asthmatic man comes in for a checkup and complains that he is having some difficulty in "starting to urinate". Physical examination indicates that the man has a blood pressure of 160/100 mm Hg and a slightly enlarged prostate. Which of the following medications would be useful in treating both of these conditions?

A. Doxazosin
B. Labetalol
C. Propranolol
D. Isoproterenol

Correct Answer = A

Doxazosin is an competitive blocker at the α1 receptor and lowers blood pressure. In addition, it blocks the α receptors in the smooth muscle of the bladder neck and prostate to improve urine flow.

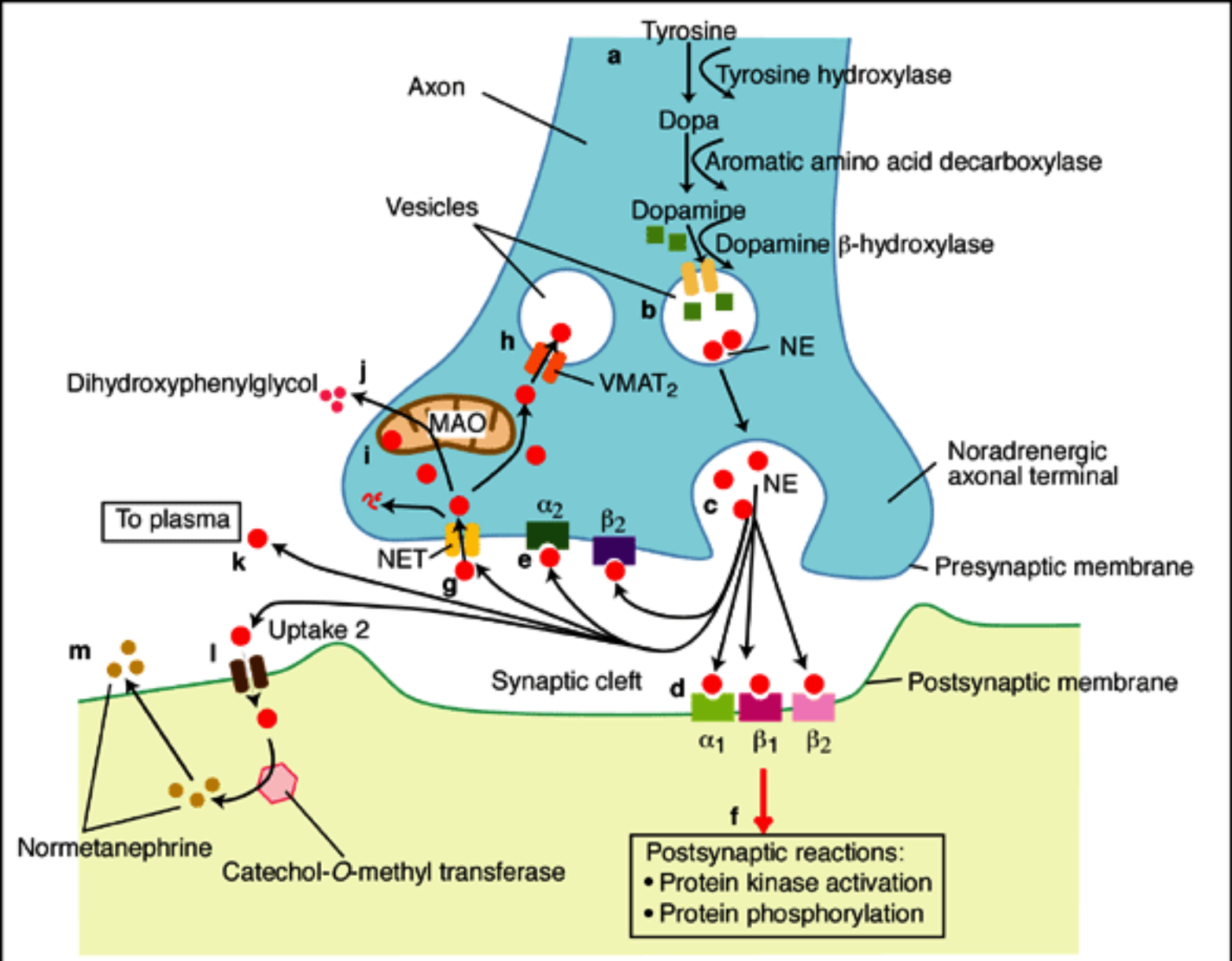
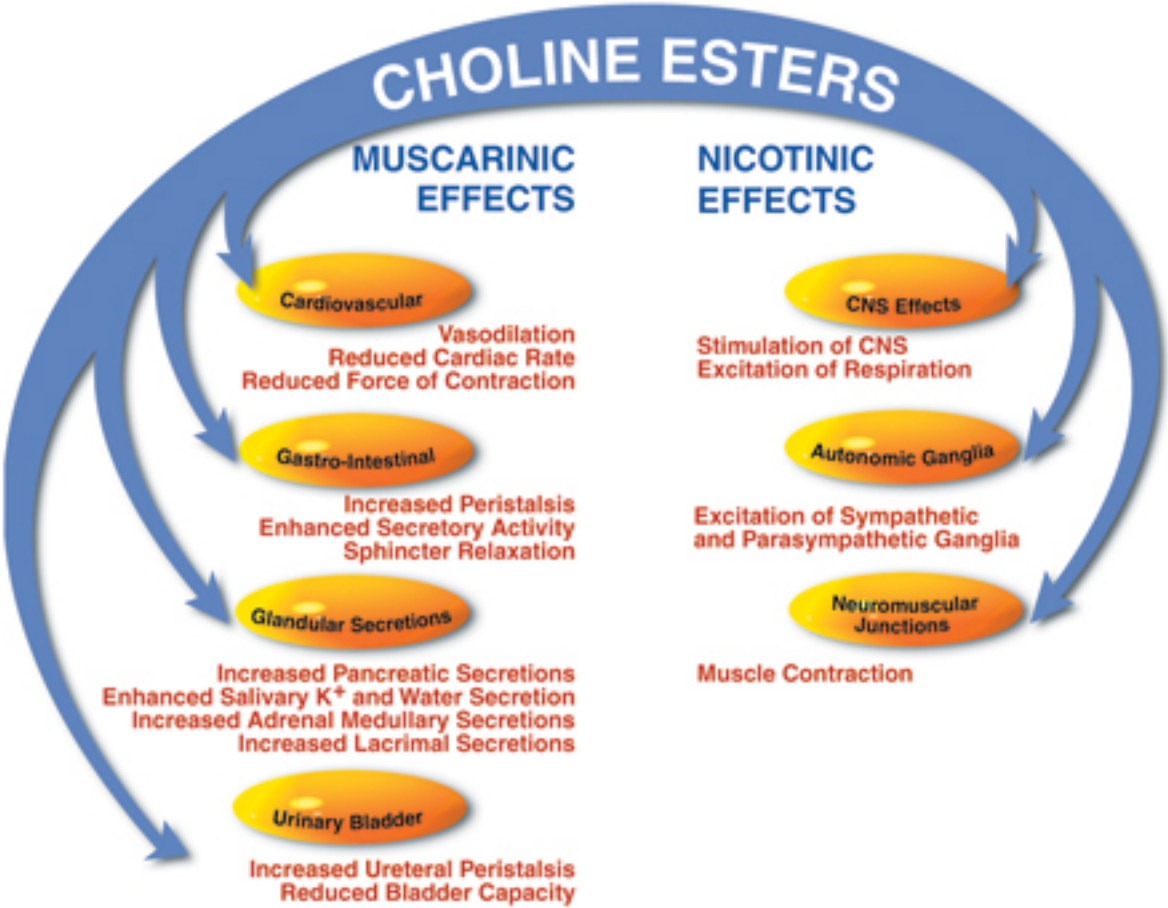


Diagram of a noradrenergic axonal terminal showing the release and re-uptake of norepinephrine


CHOLINE ESTERS
MUSCARINIC EFFECTS
NICOTINIC EFFECTS
Cardiovascular
Vasodilation
Reduced Cardiac Rate
Reduced Force of Contraction
Gastro-Intestinal
Increased Peristalsis
Enhanced Secretory Activity
Sphincter Relaxation
Glandular Secretions
Increased Pancreatic Secretions
Enhanced Salivary K+ and Water Secretion
Increased Adrenal Medullary Secretions
Increased Lacrimal Secretions
Urinary Bladder
Increased Ureteral Peristalsis
Reduced Bladder Capacity
CNS Effects
Stimulation of CNS
Excitation of Respiration
Autonomic Ganglia
Excitation of Sympathetic and Parasympathetic Ganglia
Neuromuscular Junctions
Muscle Contraction