
King Saud University
Pharmacology Team
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special Thank to those who generously shared their notes with the pharmacology team
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The criterion of the pharmacology team is to present the combination of pharmacological concepts from different lectures in comprehensible and easy to remember notes.

How do I study pharmacology for the foundation block?

Well first of all , you have to study the doctors' presentations, because it's the only authenticated source . After having a general idea about the first 3 lectures and the last lecture , you can read our notes to boost to understanding and to analytically link those lectures together .

What about lectures which is not included in the pharmacology team ?

Drug metabolism:

In this lecture you can use the work of pharmacology team 428 , which includes all the information regarding drug metabolism

Cholinergic and anti-cholinergic drug?

Due to the incompletion of the male slides , you can refer to female slides .it contains all the information in nice tables.

About the practical

Guinea pig ileum

In progress

Rabbit eye:

Yasser Alabdulakarym drew his masterpiece which covers all rabbit eye practical. If you want to study beyond that , you can study the summarization of the pharmacology team.

Pharmacology : The science deals with interaction of drugs with living system

Drugs :exogenously : Administered chemical molecules.

Pharmcotherapeutics : Application of pharmacological information together with knowledge of the disease for its prevention or cure i.e. use of drugs in treatment of disease.

Chemotherapy : Treatment of systemic infection or malignancy with specific drugs that have toxicity for infecting organism with no or minimal effects on host cells

Pharmacy : Collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances.

Pharmaceutics : Large scale manufacture of drugs.

Toxicology : Study of poisonous effects of drugs and other chemicals with emphasis on detection, prevention and treatment of poisoning .In addition to the Study of adverse effects of drugs

Molecular Aspects of Drug Actions

Drug + Molecular Target

Ion Channels

Enzymes

Carrier molecules

Receptors

*Non drug-target model:

A fifth class of drug act on NO molecular target

Pharmacologic Effect

It can be classified to Molecular level

Cellular level

Tissue level

System level

Drugs :don't work on the cell membrane

The action can be also expressed to the mechanism

Physcial action

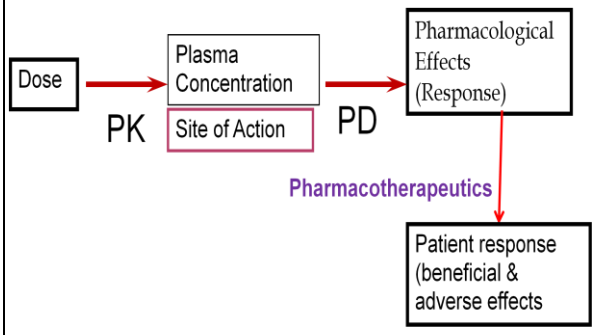
Chemical reaction

Affecting the enzyme ⇕

Outside the cell

Action through receptors

Therapeutic Response And Adverse effects

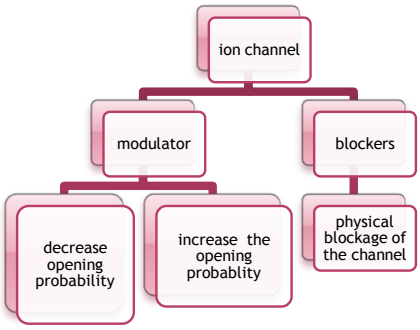


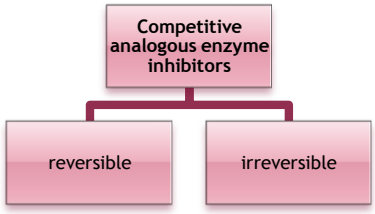
1-Pharmcodynamics :Deals with biological effects (pharmacologic and toxic) and mechanism of action of the drug

2-Pharmacokinetics is the movement of the drug in, through and out of the body to achieve drug action

Clinical pharmacology: Pharmacodynamics and pharmacokinetics investigation in healthy volunteers and in patients

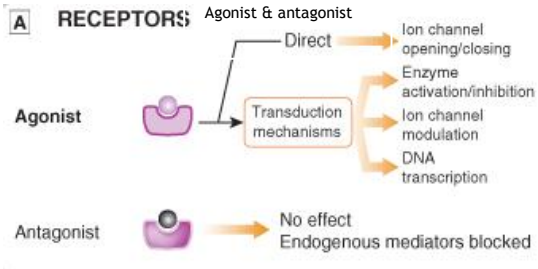
Drugs can work as





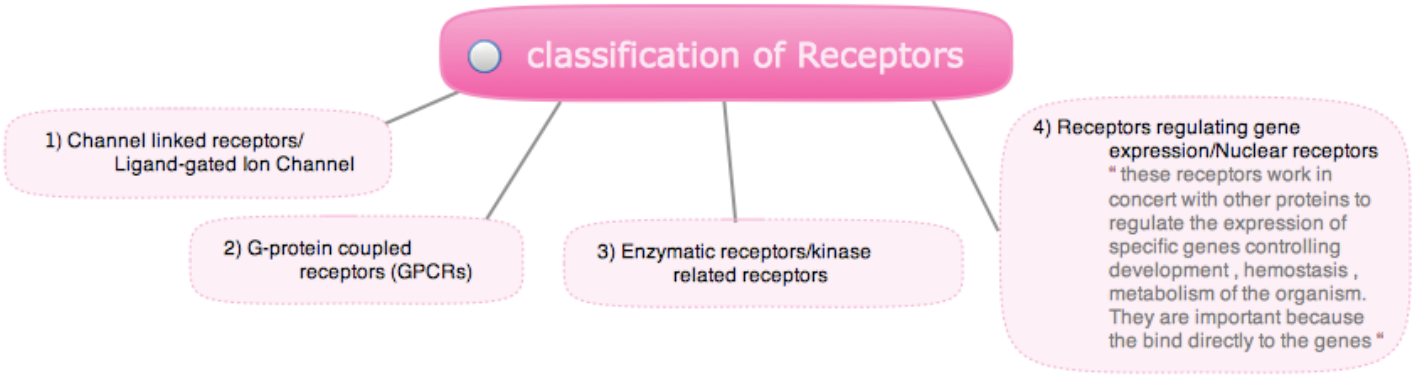
Carrier protein* inhibitors

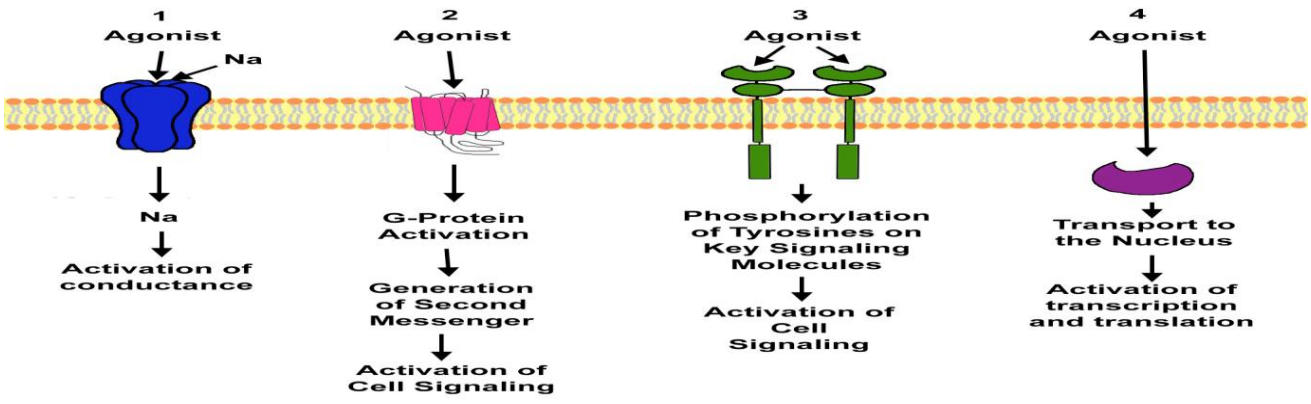
*Carrier protein molecules function to transport ions & small organic molecules. These proteins possess recognition sites can be targets for drugs where they block the transport system



*Receptors are cellular macromolecular proteins located either in the cell membrane or less frequently in the cytoplasm. They have specific recognition sites that bind selectively with a structurally-related group of synthetic drugs and endogenous mediators (ligands)

Receptor classification relies upon both molecular structure and pharmacological functional aspect





1) Channel linked receptors /Ligand-gated ion channels(ionotropic	G-protein-Coupled (Metabotropic) receptors	3) Enzymatic receptors/ kinase related receptors:	4)Receptors regulating gene expression/Nuclear receptors:
1) Channel linked receptors/Ligand-gated ion channels: - Cell surface receptors surrounds selective channels for ions (Na, K or Cl) e.g. glycine # Molecular structure of Ion channel receptor - Nicotinic acetylcholine receptor (nAChR) 1- Pentamer—made up of 4 hydrophobic membrane spanning helices of polypeptide sub-units α2,β,γ,δ chain 2- Each polypeptide cross lipid bilayer 4 times form cylindrical structure =8nm 3- ACh binds to α subunit→conformational change → channel open →ion move from outside to inside →depolarization	1- Hepta-helical (7-transmemb.spanning receptors) 2- Largest family of membrane receptors coupled to intracellular effectors system via G-protein 3- Called G-protein because of interaction with guanine nucleotide GTP & GDP e.g. mACh, adrenoceptors, DA, 5-HT, opiate receptors # Molecular structure of G-protein receptor: G-protein seven transmemb. α-helical AA segments run into 3 extrac+3 intrac. loops (extrac N-terminal + intrac C-terminal) G-protein is coupled to 3rd cytoplasmic loop Ligand binding site buried in cleft b/w α-helics or present superficially to extrac. Loop G-protein units αβγ+guanine binds to α (enzymatic activity)	The receptors functions both as recognition site (receptor) as well as an enzyme usually on the intracellular side, activated upon agonist binding Receptors consist of a single polypeptide chain of 3 parts 1-One hydrophobic membrane-inserted segment 2-Extracellular agonist-binding domain 3-Intracellular catalytic (enzyme) domain	Intracellular (cytoplasmic or nuclear) proteins respond to lipid soluble ligands +inherently capable of binding to specific gene . Therefore,it can cause stimulation or suppression of a specific m.RNA-protein synthesis is the only receptor

Drug-Receptor Interactions

Drug (D) + Receptor (R) $\underset{K_2:\ \text{dissociation}}{\overset{K_1:\ \text{association}}{\rightleftharpoons}}$ Drug complex $\rightleftharpoons$ Pharmacologic Response

(Affinity ,occupancy) (K3 efficacy, intrinsic activity)

Drugs binding to receptors follows the Law of Mass Action

The higher affinity* ↑ the lower ↓ concentration producing a given occupancy

*Affinity of a drug is its ability to bind to receptors

Fractional occupancy = $\frac{\text{Drug complex}}{\text{number of receptors}}$ =

Kd = $\frac{[D]\times[R]}{[DR]}$, KA: $\frac{[DR]}{[D]\times[R]}$ D, drug R, receptor DR, drug receptor complex

Kd : is an intrinsic property for any given receptor-drug pair

Kd(A) ; dissociation constant is the concentration of the ligand at which 50% of the available receptors are occupied

The curve of drug concentration versus drug response is sigmoid – S shaped curve

Potency :presented as the concentration or dose needed to produce a 50% maximal response (EC50 or ED50)

Efficacy (max response) is the max response the drug can produce (Emax)

Efficacy of an agonist depends on both affinity (binding) & intrinsic activity

Intrinsic activity is any factor that interacts with the production of a pharmacological response i.e Intrinsic activity (Efficacy) is the ability of the drug to activate the receptor

Some receptors are stable more in active state in absence of endogenous or exogenous agonists

Inverse agonist decrease the activity of receptors by changing their conformation.

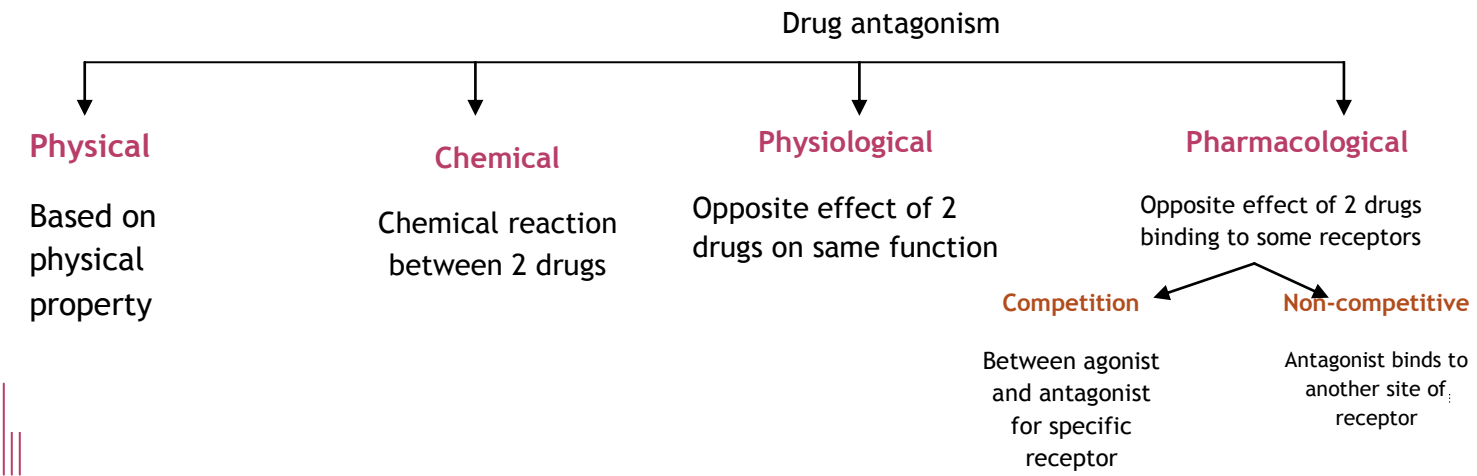
Quantal responses include effects that are either present or not, such as vomiting, sleeping, bleeding etc

Therapeutic index = $\frac{\text{Lethal dose}}{\text{lethal effect}}$, TI = LD50/ED50

Drugs with higher ↑ Therapeutic index are safer ↑ and vice versa

Correlations of agonist and antagonist

Full agonist drugs	Partial agonist drugs	Antagonist drugs
High affinity & High efficacy	High affinity & low efficacy	High affinity & non efficacy



UANTITATIVE ASPECTS OF DRUG ACTIONS

Quantitative aspects are important for mode of use

e.g. dose-response relationship

	Graded Dose-Response	Quantal Dose-Response
Type of study	Vitro	vivo
Plotted	Curves → hyperbolic; Sigmoid-shaped	Curve → Log-does percentage; Gaussian distribution
Valuble data	ED_{50}/EC_{50} (median effective dose or concentration): Dose or conc. which produces 50% of maximal response Drugs with same action at a receptor but with d/f potency show parallel DRC Potencies of two drugs can be compared by ED_{50} ED_{100}/EDmax (ceiling effect): Conc. which produces maximal response	Median Effective Dose (ED_{50}) : Dose of a drug required to produce 50% of maximum response Median lethal dose (LD_{50}): Dose of a drug required to kill 50% of experimental animals; measurement of toxicity Median toxic dose (TD50) : Dose producing toxicity in 50% animals or humans Margin of safety Ratio of $LD_{0.1}$ / $ED_{99.9}$:$LD_{0.1}$=min. lethal dose for 0.1 % of population; $ED_{99.9}$%=minimum effective dose for 99.9 % of population

Desensitization …

. Some Cells of tissues..exposed to some drugs .. these tissues become Desensitized

Desensitization (Tachphlaxis) …

When the tissue become less response .

This process has potential clinical significance

Because:It may limit the therapeutic response of the drug..

Often the drug effect may gradually diminishes when it's given

- Continuously
- Repeatedly

Some Mechanisms function occure

- Relatively slowly
- Over the course of hours or days
- Quickly within minutes

Other relative terms:

Tolerance : more gradual (needs time) decrease in responsiveness

Refractoriness: used in relation to a loss of therapeutic efficacy

Drug resistance : loss of effectiveness of a drug like (antimicrobial or anti-tumor drug)

Agonist: any drug that activate that receptor

Mechanism of Desensitisation

→ **Change in receptors**

2 kinds of receptors

1- Ionic channel
The drug reached those channels,, but they don't open
2- G-protein
Drug may do coupling with G-protein but the G-protein dose not do any action
It's caused By conformational change in R , resulting in tight binding of the agonist molecule without the opining of the ionic channel
It usually takes few minutes to develop and recover

→ **Loss of receptors**

Receptors become reduced in number because of exhaustion it caused of

1- Internalization (become destructed in the cell)
2- Endocytosis (eaten by the cell itself)

By Degradation of those receptors .. When this process occur faster than it's synthesis ..the receptors are reduced ..that's why the response is reduced too ..

It's common in Hormone (Taking hormones for prolonged period of time cause desensitization of the receptors)

→ **Exhaustion of mediators**

Due to depletion

EX:amphetamine which release amine from nerve terminal

→ **Altered drug metabolism**

- In the liver

After the drug do its effect it become released by the body .

Chytochrome P_{456} : is an enzyme in the liver responsble of drug degradation

EX: Barbiturate (sleapness helper) … Ethanol (Cohol)

When taking to much of Alcohol the body become tolarnce

Tolarnce to nitrovasodilation result mainly from decrease metabolism ..

Nitric oxide : medaiator which responsble of vasodilation in our body

→ **Physiological adaptation**

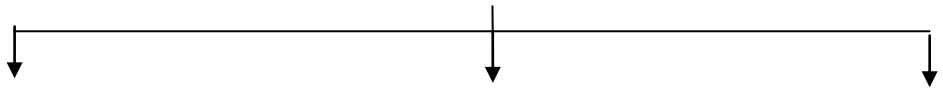
Diminution of a drugs effect may occur because of opposed by a homeostatic response .

EX: BP lowering effect of (thiazide diuretics= substance helps in getting rid o water and nacl) limited because of gradual activation of renin-angiotensin system (keeping th water and nacl)

Adverse Drug Reaction (ADRs) :

Harm and unpleasant effect of the drug ..at a ***NORMAL DOSE***

Types of ADRs



Type A = Augmented	Type B = Bizarre	Type C = Chronic effects
It occur because of: pharmacological effects .. Related to its function Occur in all patients but may vary from one to another EX:propranolol and	Related to different pathway And it gives a reversiable effect	Long term use accumulation of the drug in the body EX:ocular toxicity with antimalarial

Seriousness and severity of ADRs :

- Death
- Life-threatening
- Hospitalization
- Disability
- Congenital anomaly (Drugs which are used during pregnancy)

ADRs unrelated to the main pharmacological action of the drug :

- Predictable when taking excessive does of a drug paracetamol (panadol)
  - Hepatotoxicity >> live poisoning
  - Tinnitus Ear resonance
  - Aminoglycoside ototoxicity Ear
- During pregnancy
  - Teratogenicity >> embryo-deformation
- Anaphylaxis response to penicillin
- Immunologic reaction
- ADRs may result from decrease drug clearance (removal out of the body) in patient with renal(urine) or liver(feces)>>>Drug-drug reaction

Pharmacological formulas

- Kd = $\frac{[D]\times[R]}{[DR]}$, KA: $\frac{[DR]}{[D]\times[R]}$ >>>>> D, drug R, receptor DR, drug receptor complex
- Kd is constant and intrinsic property for any given receptor-drug pair >> 

- Bio = AUC oral/AUC IV x 100
- VD = Dose/Plasma Concentration >>>> Units: L and L/Kg
- Cl =the volume of blood/fluid cleared of drug per unit time or CL = kVD >>> Cl , clearance K , elimination rate constant
- E =$\frac{v\,max\,\times c}{km+c}$ >>> E , elimination v max The maximum initial velocity or rate of a reaction. C , substance concentration Km = Michaelis constant
- Loading dose = target plasma concentration × VD >> VD = Dose/Plasma Concentration
- Maintenance Dose = CL x target steady state drug concentration >>> Cl , clearance
- Half-life is the time taken for the drug concentration to fall to half its original value
- The elimination rate constant (k) is the fraction of drug removed per unit time
- Steady-state occurs after a drug has been given for approximately 4-5 t1/2 >>> t1/2 half- life

ADRENERGICS and ANTIADRENERGICS

Acetylcholine is the predominant neurotransmitter in all pre-synapse -sympathetic or parasympathetic-and the parasympathetic post-synapse

Acetylcholine is ion gated -fast transmitter - which can cause damage of muscles .Therefore ,the duration of acetylcholine action is within milliseconds , due to its destruction by **cholinesterase**. .

Unlike acetylcholine, the duration of norepinephrone action is longer because is NOT ion gated - G protein -

Cholinergic system maintain the adrenergic system **BUT Not** vice versa

Cholinergic receptors - in all parasympathetic synapse

Nicotinic receptors	muscarinic receptors
ion gated	G-protein -second messenger-
For fast and immediate action	Longer duration action

Adrenaline is the neurotransmitter in the sympathetic post-synapse

adrenaline = epinephrine with methyl group

noradrenalin = norepinephorine >>>> without methyl group

The synthesis of norepinephrine

Tyrosine → (hydrolysis inside the cell) DPOA → Dopamine → norepinephrine -NE-

The Dopamine is stored to protect if from being destructed in the cytoplasm

After the release of NE from the pre-synapse it binds to the receptors in the post-synapse then action occurs

After that , NE is reuptaken through autoreceptors to the pre-synaptic cytoplasm.

*Some drugs works as inhibitors of the autoreceptors to increase the concentration of NE ,such as antidepressants .

Pre-synaptic receptors inhibits the release of NE

Table 6–3. Characteristics of some important adrenoceptors in the ANS.

Receptor	Location	G Protein	Second Messenger	Major Functions
α_1	Effector tissues: smooth muscle, glands	G_q	↑ IP_3, DAG	↑ Ca^{2+}, causes contraction, secretion
α_2	Nerve endings, some smooth muscle	G_i	↓ cAMP	↓ Transmitter release, causes contraction
β_1	Cardiac muscle, juxtaglomerular apparatus	G_s	↑ cAMP	↑ Heart rate, ↑ force; ↑ renin release
β_2	Smooth muscle, cardiac muscle	G_s	↑ cAMP	Relax smooth muscle; ↑ glycogenolysis; ↑ heart rate, force
β_3	Adipose cells	G_s	↑ cAMP	↑ Lipolysis
D_1	Smooth muscle	G_s	↑ cAMP	Relax renal vascular smooth muscle

α 1 receptor is in the blood vessels mainly veins . its stimulation causes contraction which leads to high blood pressure.

α 2 receptor is the only auotreceptor decreases . its stimulation decrease the release then causes low blood pressure ‘

β 2 receptor is in the bronchi . its stimulation causes bronchial dilation

vagus receptor is cholinergic which decrease the heart rate , the opposite of beta 2

catechol amine >> 2 OH + amine .....eg epinephrine

non- catechol amine >>> just amine

dopamine without hydroxyl group

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adrenaline

- short half life
- not given orally
- not selective
- relatively selective
- when using high dosage results in loose of selectivity
- isoprenaline acts on beta 1 ,2 ,3 only