ADRENERGIC Agonist

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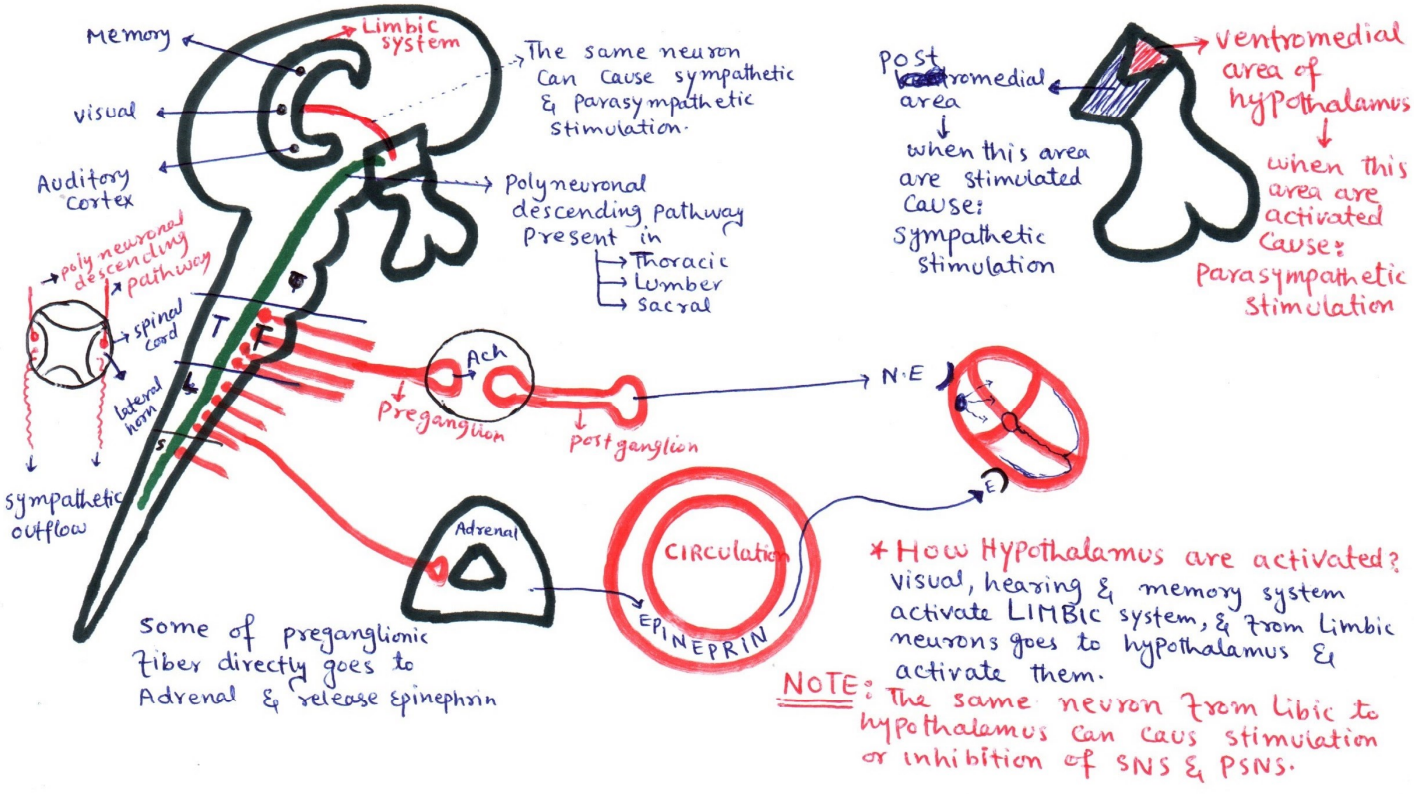
FROM: Dr. Najeeb lecture

ANS Pharmacology

- Drug Acting on SNS
  - Sympathomimatic Drugs OR Adrenergic drugs OR Adrenergic Agonist
  - Sympatholytic Drug OR Anti Adrenergic drugs OR Adrenergic Antagonist
- Drugs acting on PSNS

* When there is suddenly increase in stress, sympathetic Nervous system will fire, and prepare the body for fight & flight.
* Normaly sympathetic & Parasympathetic opposing each other.



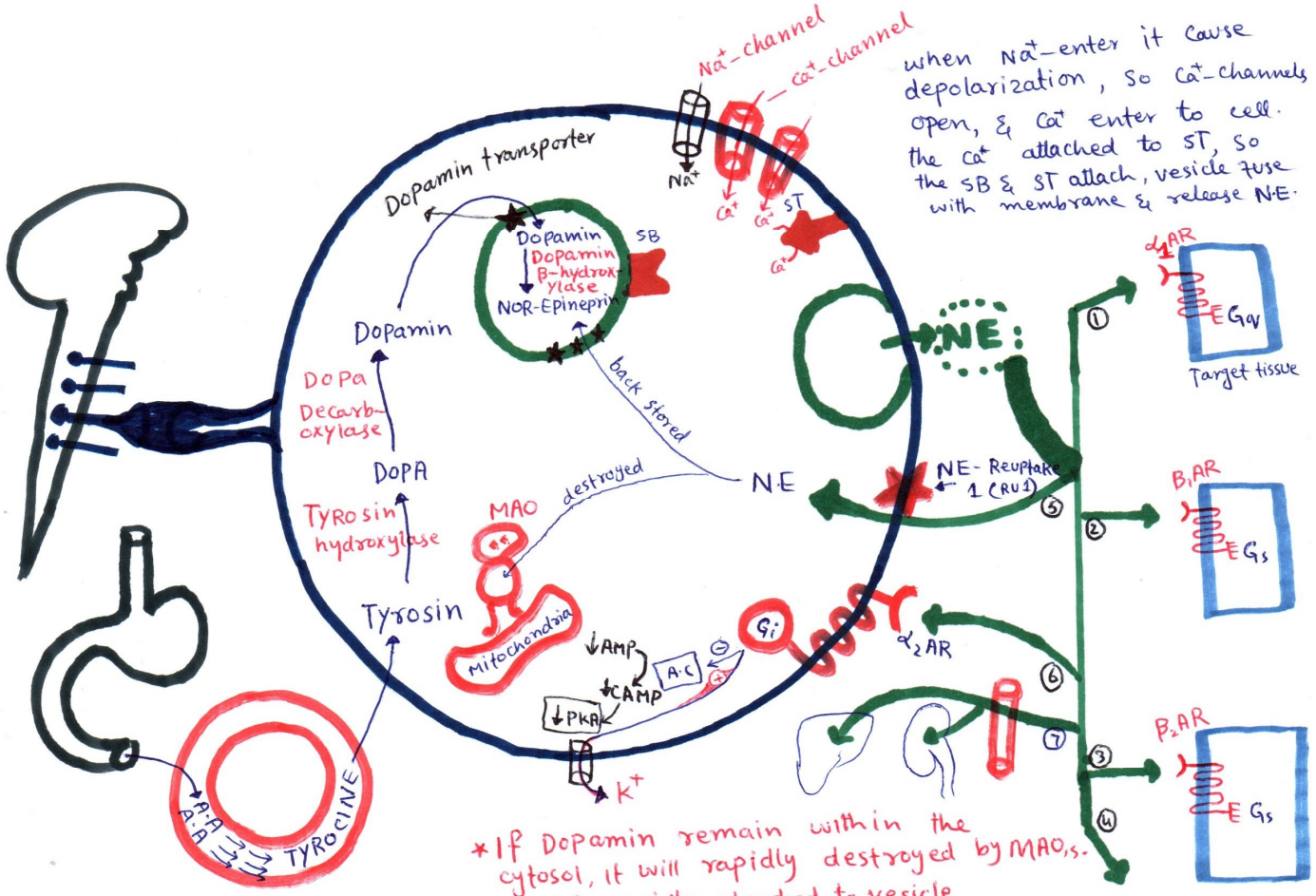
* How Hypothalamus are activated? visual, hearing & memory system activate LIMBIC system, & from Limbic neurons goes to hypothalamus & activate them.

NOTE: The same neuron from Libic to hypothalamus Can caus stimulation or inhibition of SNS & PSNS.

Preganglionic ⟶ Release Ach

Post ganglionic ⟶ Release Nor Epinephrine

All neurons from CNS comeout (Release Ach) are cholinergic.



when NE Released

* 80% of NE are reabsorbed by NE-Reuptake-1 (RU1) when done its action.
* (NE-RU1 is Na+/Cl- dependant)

when α_2 AR of nerve ending are stimulated by NE, it bind with Gi, so inhibit A.C as a result cAMP↓, → ↓ P.K.A, so K+ channel open, cell become -ve, release further N.E are ↓es.

NE-Reuptake-1 are inhibited by → TCA (Imipramin), SNRI (Duloxetine), Cocain

COMT

Cathecol-o-methyl Transferase

↓

It convert N.E to inactive

NOTE: Reuptake of NE into neuronal membrane is the primary mechanism for the termination of this effect

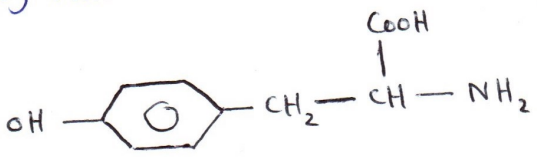
Removal of NE

① diffuse out & enter to circulation
② inactivate by COMT
③ Back Reuptake (Main Mechanism)

Reuptaked NE

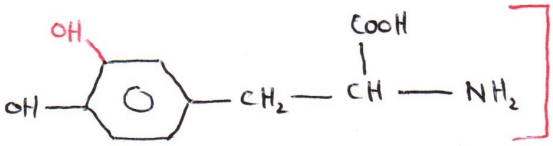
① back to vesicle
② destroyed by MAO

In pharmacology The Biochemistry of only ANS Drugs are important

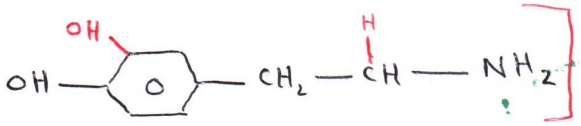


Any benzene ring with 3rd or 4th position have OH are Called Cathecol Ring

Cathecolamine Compounds with amine group & Catecol ring:



DOPA



DOPAMINE

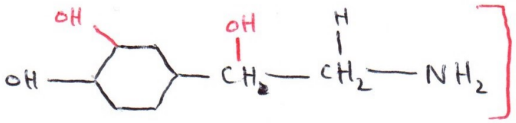
If dopamin remain in cytoplasm, it will destroyed by MAO (Monoamineoxidase), so to save it, it is immediately Transport into neuronal vesicle

* what are Monoamines:

Neurotransmitters which are derivitive of single aminoacid.

* Tyrosine make many monoAmines like:

① Dopamine, ② Epinephrin ③ Nor-epinephrin ④ Tryptophan → (serotoni



Nor- epinephrine

* Ach is not monoamine

Nor-Epineperine is bound with protein called Chromogranin OR with ATP or Ascorbic Acid, & all bound norepinephrine act as osmotically as a singal molecule.

How Nor-Epinephrine are Released?

Nerve ending have Depolarizing sensitive Ca^+-channel

So, when Depolarization occur Na^+ move in, so Ca^+ channel are activated & Ca^+ move in and allow vesicle to fuse with neuronal membrane.

Vesicle have a protein called "Synapto Bravin" and neuronal membrane have a protein called "Syntaxin", the syntaxin have an obstruct, when Ca^+ come and bind with obstruct, both Ca^+ will repell each other, so syntaxin will opens

so the synaptobravin come & fuse with syntaxine & the Nor-epinephrine release from the nerve ending by fusing vesicle with neuronal membrane. This vesicle is pulled again by clathrin & ready for again use.

ADRENERGIC RECEPTORS

All Adrenergic receptors are 7pass protein

* α_2 A.R ⟶ presynaptic nerve membrane
* α_1AR, β_1AR, β_2AR ⟶ postsynaptic membrane (tissue)

When N. Epinephrine are released, small amount of it acts on α_2AR So, cAMP level les, Gi proteins also open the K^+-channel & intracellecular K^+ comes out.

& cell become hyperpolarized such cell is different to polarized, so nerve ending is inhibited; further release of nor-epinephrin is reduced, this mechanism is AUTO inhibitory.

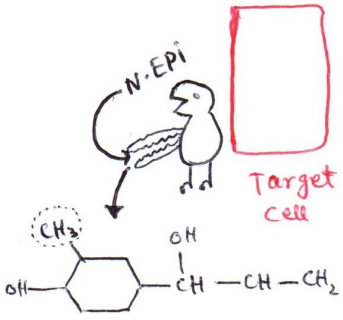
↓ cAMP lead to reduce activity of protein kinase-A (P.K.A), so synthesis of neurotransmitter are reduced, so:

* α_2AR act as an autoinhibitory Molecule.

whatever nor-epinephrine is released 80% of it is restore to reuse. As N.Epinephrine is uptaken, small amount of it, which is still not taken to vesicle, are destryoed by MAO.

* N.Epi is taken back by Reuptake-1 mechanism.

N.Epi is also acted upon by another Enzyme **COMT** present on postmembrane and remove OH group N.Epi & add CH_3 group to it.
Due to methylation, this molecular become less polar
This enzyme is also present in the liver.



very small amount of N.Epi is diffuse into general circulation & destroyed by Liver & Kidney.

sympatholytic Drugs

1) METHYL TYROSINE: enter into nerve ending & capture Tyrosine hydroxylase, so enzyme can't work for normal pathway (CH_3—Tyrosine is structural analoge of Tyrosine)
Total N.Epi activity is ↓ed.
So this drug is sympatholytic drug.

(2) RESERPINE:

This Drug inhibit Dopamin Transporter (*), So dopamin canit be enterd into vesicle, the vesicle remain Empty. Dopamin is destryed by MAO.

* This drug also inhibit uptake of Epi & N·Epi by vesicle.

* Initially this drug is used as Anti hypertensive, but now adays it is not used as antihypertensive.

(3) Guanadril OR Bretylium:

this drug does not allow the fusion of vesicle with nerve membrane, so the neurotransmitter are not released.

(4) α-methyl Dopa:

Funny Example: sometime we like a girl, when we know, she is not a girl but shemale.

α-methyl dopa is taken by nerve ending membrane, & dopa decarboxylase act on it & make α-methyl Dopamin from it.

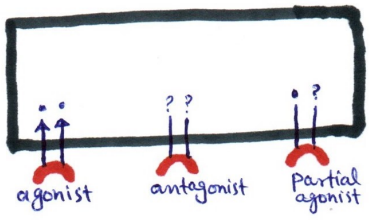
α-methyl dopa —(α-methyl dopa decarboxylase; Co_2)→ α-methyl Dopamine

α-methyl dopamine enter into vesicle & converted into α-methyl · N·Epi

α-methyl dopamin ⟶ α-methyl N·Epi

So, when Action potential comes, α-methyl Nor-Epinephrine is come out but real action is not there, so sympathetic activity goes down.

* **Agonist**: bind to receptor & stimulate it.
* **Antagonist**: bind to receptor but doesnit stimulate it.
* **Partial agonist**: bind to receptor & stimulate MUCH.
* **Partial antagonist**: bind to receptor but doesnt have full action.
* **Mixed agonist antagonist** bind to one site & stimulate them, while bind to other side & canit cause stimulation



ADRENERGIC RECEPTOR AGONIST

- α
  - $\alpha_1 \cdot \alpha_2$
    - phenoxybenzene
    - Phentolamine
  - α_1
    - Prazosine
    - Terazosine
- β
  - $\beta_1 \cdot \beta_2$
    - Propranolol
  - β_1
    - Metoprolol
    - ATENelol

If these drugs are given in high Concentration also block β_2

difference B/w phenoxybenzen & phentolamine

* Phenoxybenzene = Irreversible non Competitive receptor blocker.
* Phentolamine = Reversible Competitive receptor blocker.

difference B/w Prazosine & Trazosine

* Prazosine = short half life.
* Trazosine = long half life.

* drug which reduce synthesis of Neurotransmitter → Methyl tyrosine
* drug which block storage of Neurotransmitter → Reserpine
* drug which block the release of Neurotransmitter → Guanadril OR Bretylium

Sympathomimitic Drugs

Directly acting agonist

Drugs which directly stimulate the Post synaptatic receptors & alter the synthesis of *Epinephrine

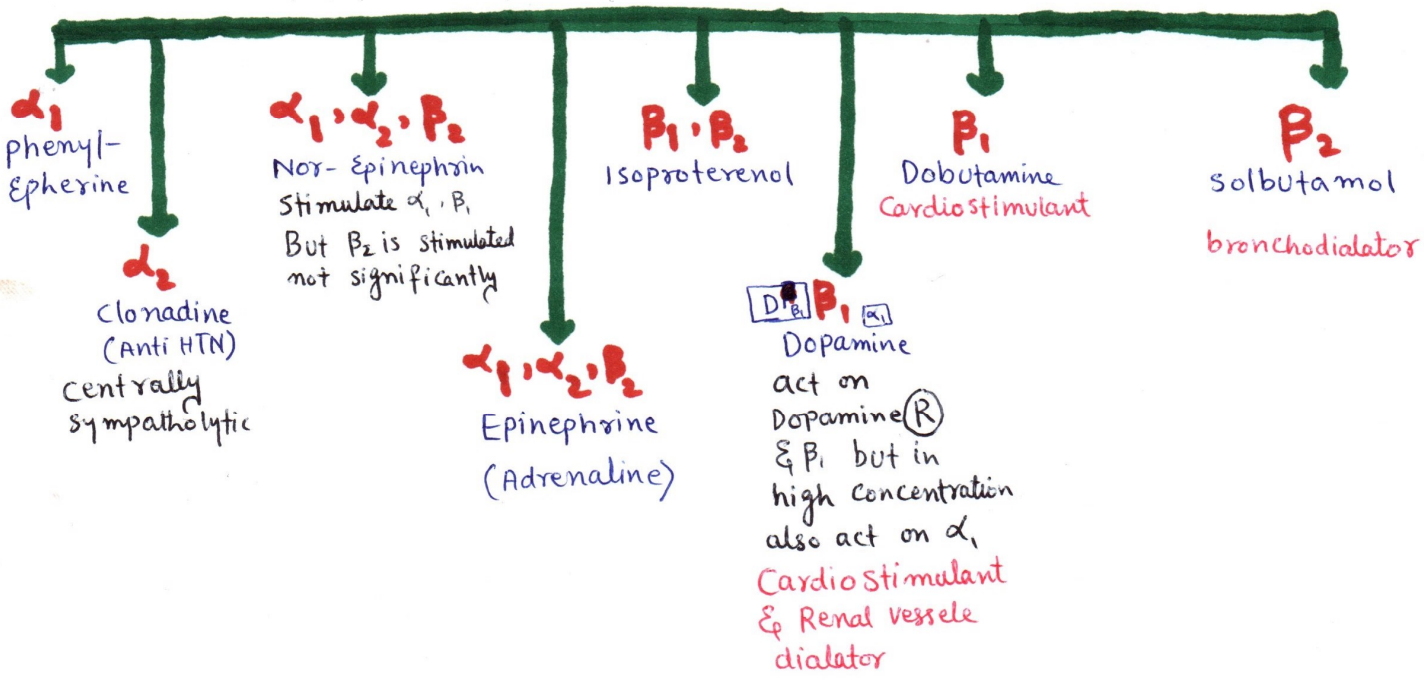
α_1 α_2 $\alpha_1\alpha_2$ $\alpha_1\beta_1\beta_2$ $\beta_1\beta_2$ β_2

* Drugs which stimulate α_2 receptor → ↓ the release of N·E
* Drugs which block α_2 AR basically ↑ the release of N·E

Indirectly acting drugs

Drugs which act on sympathetic nerve ending & cause stimulation.

DIRECTLY ACTING DRUGS



INDIRECTLY ACTING DRUGS

1) Cocain: Act with reuptake-1, so NeuroTransmitter are not reuptake by nerve ending.
* It remains in synaptic cleft for longer time, so act on receptor for longer time.

2) Tricyclic Anti depressant: Bind with reuptake-1 but not strongly & slightly reduce reuptake.

3) Selective serotonin Reuptake inhibitor (SSRI) e.g: Prozaic

4) Pargyline, Prenylcipromide: These are MAO's inhibitor used as an antidepressant.

5) Amphitamines, TYRamine: These drugs Enhance fusion of Vessele with membrane & release Neurotransmitters.

Biological Responce to stress under sympathetic

Tissue & organs to be stimulated

* α_1 Adrenergic Receptor
* β_1 Adrenergic receptor

All the tissues to be stimulated have α_1 AR Except

① β_1 Heart

② β_1 Juxta glomerular Apparatus

③ β_3 Adipocytes

β_3 is modified β_1

Tissue & organ function inhibited

α_2 Adrenergic receptor

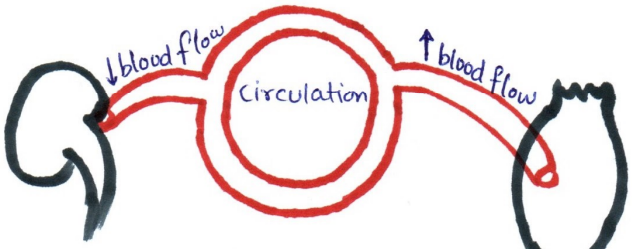
β_2 Adrenergic receptor

All the tissue to be inhibited having β_2 AR EXCEPT:

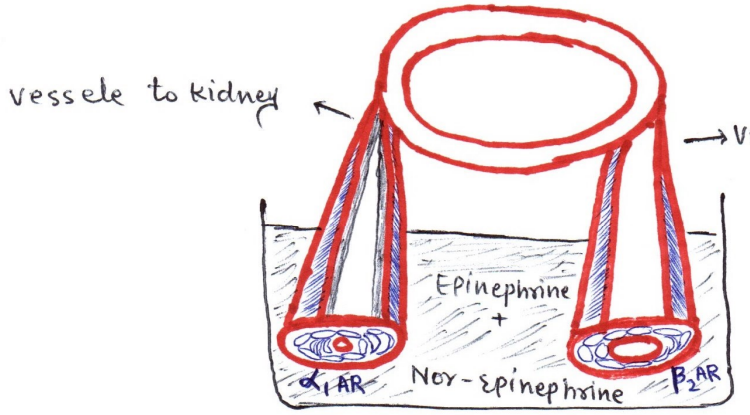
① Presynaptic nerve ending α_2 AR

② platlet α_2 AR

③ Insuline producing cell β_2



when a person run, blood flow to muscles ↑es, and blood flow to kidney ↓es b/c kidney vessele have α_1 AR on smooth muscle, so stimulated & Constricted, Muscle have α_2 AR, so inhibeted & Relaxed.

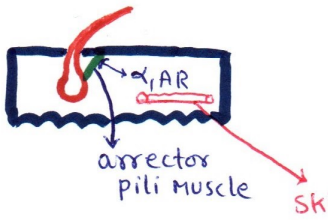


If we put a renal vessel & Muscle vessele in a container having Epi, N·E, the renal vessele will constrict & Muscle vessele are dialated.

* All the tissue & organs which fight with stress have stimulatory receptor e.g: α_1 & β_1
* Tissue, which does not fight with stress have inhibitory receptor. e.g β_2, α_2

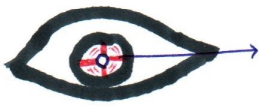
what are changes in body under influence of Adrenergic system.

1) HAIR



Hair straight up b/c of Stimulation of arrector pili Muscle, which has α_1AR

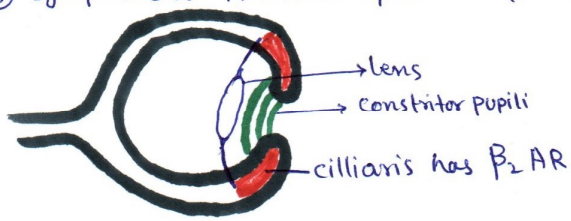
2) EYES



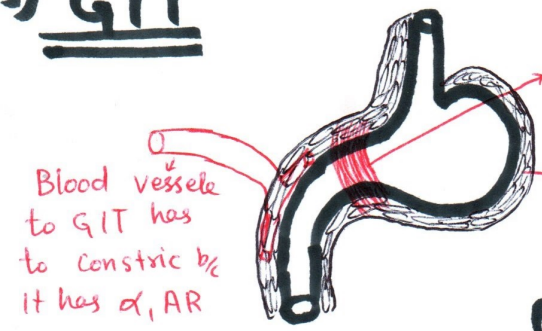
Dialator pupili are stimulated, cause pupil Constriction.
↳ α_1AR

ⓐ pupil ⇒ Constriction

ⓑ sympathetic Nervous system focus the eye for far vision.
(lens become thin)



3) GIT

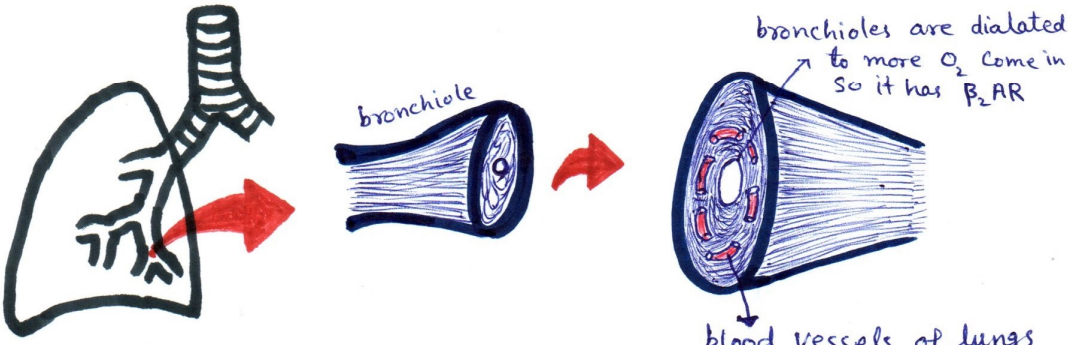


Circular Muscles
* sphincters has to constric b/c has α_1AR

Longitidunal Muscles
* smooth Muscle has to relax has β_2AR, b/c in stress no need for peristalsis
* secretions also decreased.

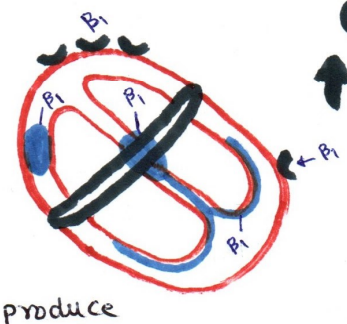
Blood vessele to GIT has to constric b/c it has α_1AR

4) Lungs



⑤ CVS

SV ⇒ Vol of blood ejected by ventricles during one pump.



CO = SV · HR

↑CO = ↑SV · ↑HR

Heart have many β_1 receptors

ie on SA-node, AV-node, purkinji system, atrial & ventricular myocardium.

Automaticity ⇒ property of tissue to produce depolarization spontaneously

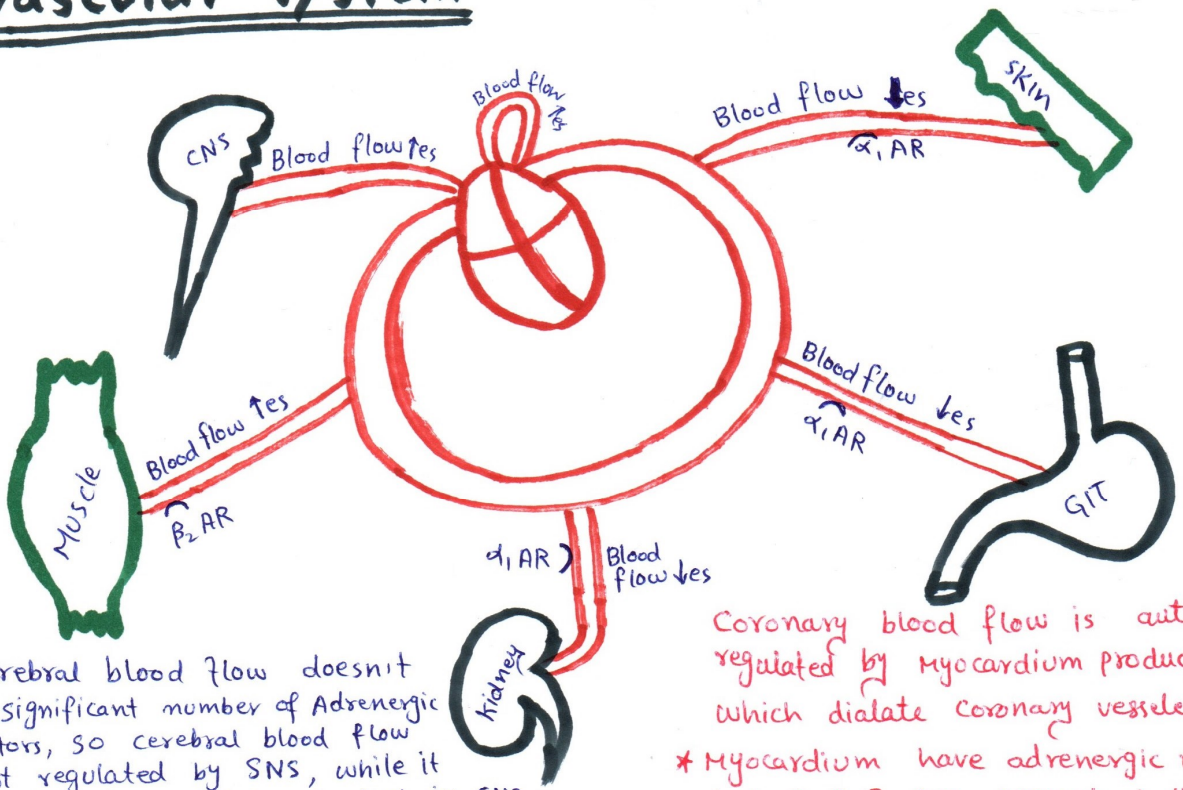
SA-node produce Automaticity

* SA-node have +ve chronotropic action on drug.
* AV-node have +ve Dromotropic action on drug.

↑Contractility is called +ve Inotropic action, SV is ↑ed by Inotropic action.

So sympathetic nervous system ↑es Cardiac output.

6) vascular system



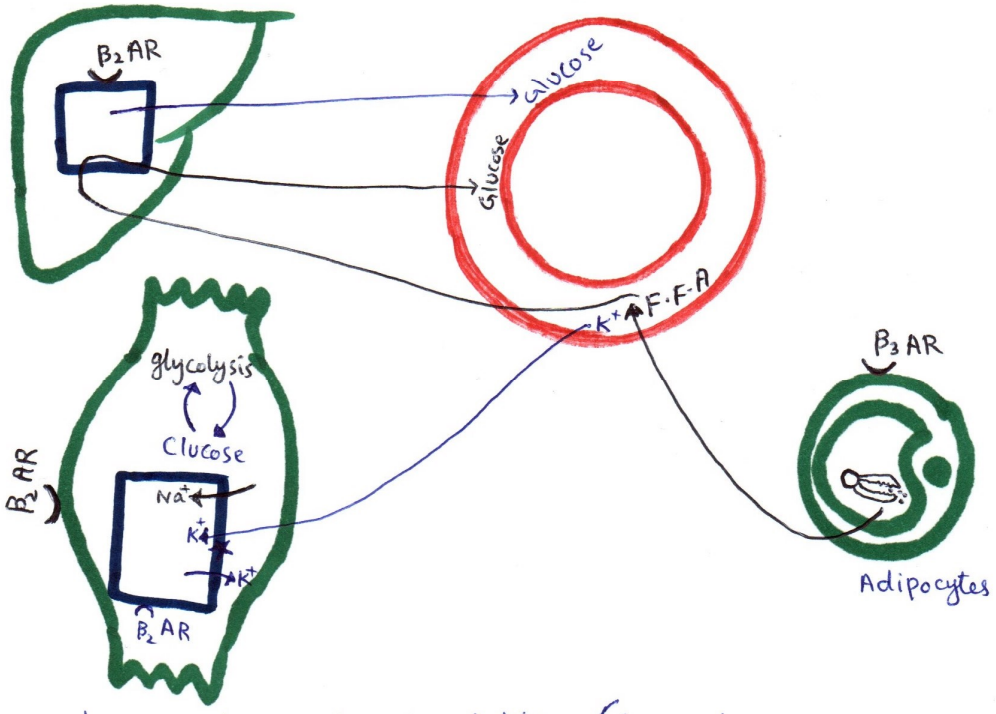
* Cerebral blood flow doesn't have significant number of Adrenergic receptors, so cerebral blood flow is not regulated by SNS, while it is regulated by metabolic product in CNS itself, when CNS stimulated more metabolite produced so ↑ CNS blood flow.

Coronary blood flow is auto regulated by myocardium products, which dialate coronary vessels.

* Myocardium have adrenergic receptor but α_1 & β_1 are present at the same rate, & these receptors are stimulated according to ventricle work.

7) METABOLIC changes

one of the most important function of the liver is to take Glucose & Convert it into glycogen.



① Liver release glucose to circulation (ie: glycogenolysis)

② Adipocytes ⟶ Lipolysis

③ Gluconeogenesis ⟶ F.F.A ⟶ Glucose

④ Na^+—K^+ ATPase is activated & cell start taking K^+ from blood.

β_2 receptor on Muscle fiber is activated it will stimulate Na^+—K^+ ATPase

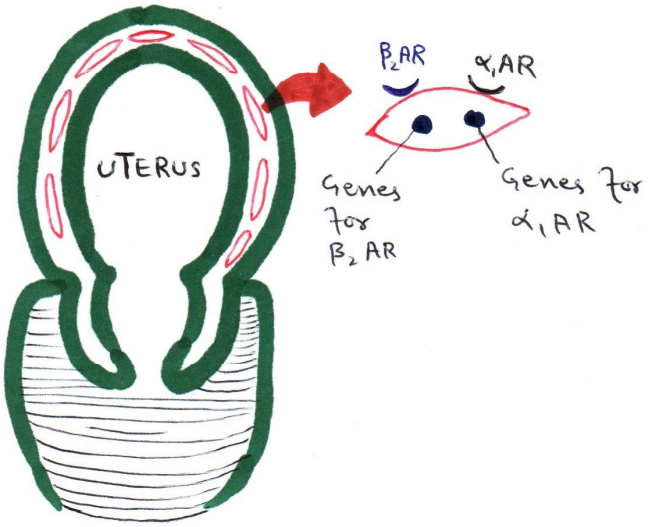
* within the Muscle glycogenolysis occur.

Muscle spindle also have β_2 receptor, so under increased sympathetic flow β_2 receptor are stimulated no proper Extensor & flexor Muscle tone is present, so musle tremor occur. e.g during fear. b/c loss of Equilibrium.

* Glucose level in the blood ↑es ⟶ K^+ level in the blood ↓es.
* FFA level in the blood ↑es * Muscle glycogenolysis occur.

8) sympathetic action on urogenital system

Myocardium have Genes for β_2 & α_1 AR.



* when female is not pregnant, & is under the influence of Estrogen & progesteron during monthly sexual cycle, α_1 AR genes are expressed & increase the way for Conception.

* when female become pregnant genes for β_2 will be expressed, so pregnant female have more β_2 receptor on uterus than α_1AR.

Rightrodrine will act on β_2 and prevent premature baby delivery.

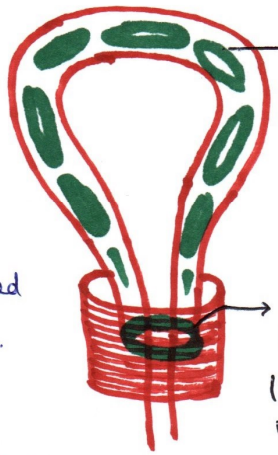
* female Excretion & secretion are neurologically controlled by the same way. is parasympathetic Nervous system.

* female Ejaculation & orgasm are Controlled by sympathetic Nervous system.

Male

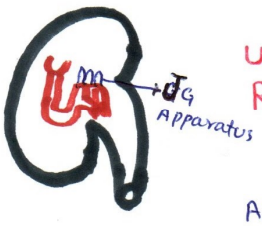
Ejaculation = sympathetic N.S.

ejaculatory duct, vas defference, prostate ..... etc are stimulated & controlled, so they have α_1AR.



Detrosure Muscle has β_2AR, so during stress it relaxes.

Internal urethral sphincter has α_1AR, so during stress it constrict to prevent Urination.



Under stressful conditions
Renin ↑es → Ang II ↑es which cause:
* Venoconstriction
* Release of Aldosteron → ↑ Na^+ & H_2O retention.

Ang II is 1000 times more powerful vasoconstrictor than Epi/N.E
* Drugs which slightly reduce Ang II are used to controle BP.

Characteristic Physiological & Pharmacological Action by Stimulation of specific Adrenergic-R

α_1 AR

ⓐ Vascular Smooth Muscle
⇓
Vasoconstriction

ⓑ Mydriasis

ⓒ ↑ Piloerection

ⓓ Constriction of prostate smooth muscle

ⓔ Constriction of internal urethral sphincter

α_2 AR

ⓐ on presynaptic nerve ending α_2 AR
⇓
decrease N·E release

ⓑ decrease insuline release

ⓒ ↓es Lipolysis from Adipocytes

ⓓ platlet aggregation

β_1 AR

Heart

- *SA-node
- *AV-node
- *Purkinji
- *Atria
- *Ventricle

- +ve chronotropy
- +ve Dromotropy
- +ve Bathmotropy
- +ve inotropy
- +ve clinotropy

Kidey

Guxta glumerular Apparatus

β_3 AR Adipocyte

drug which stimulate β_1 AR Cause ↑ Lipolysis

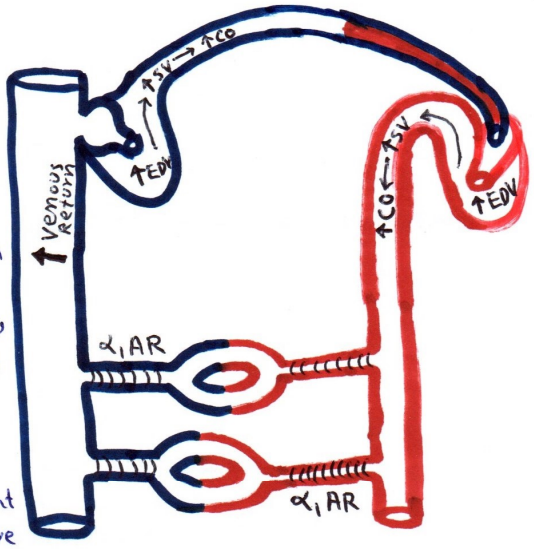
β_2 AR

ⓐ bronchial smooth musd
↓
Bronchodialation

ⓑ Vascular Smooth musd
↓
Vasodialation to skeletal Muscles

ⓒ Myometrium of Pregnant uterus
↓
Relax Uterus

ⓓ Liver
↓
↑ glycogenolysis



arteriole have α_1 AR, so by stimulation, arterioconstriction occurs.
specially splenic, renal, cutaneous there is ↑esd Total perephral resistance, it become different for blood to move from arterial to venous side

Vascular smooth muscle
↓
Vasoconstriction

Venoconstriction
↑ Venous Return
↑ EDV
↑ S.V
↑ Co
↑ systolic BP

Arteriolo constriction
↑ T.P.R
↑ Diastolic BP

* Pressure in artery during diastole is totally depend on T.P.R

* ↑T.P.R in arteriole ⟶ ↑es diastolic BP
arteriole act as a tape, when tape is open pressure in pipe ↓es.

* Co ∝ systolic BP

* Diastolic ∝ T.P.R

$BP = \frac{\text{systolic}}{\text{diastolic}} = \frac{Co}{T.P.R}$

* Why venous vessele are capacitance vessele?
B/c 10% blood volume is present in venous side.

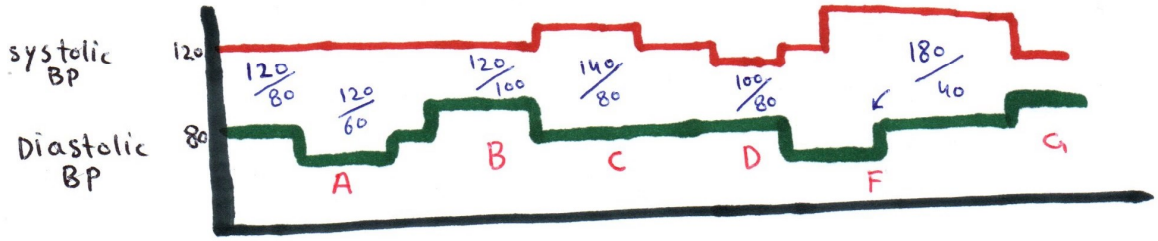
Systemic BP = $\frac{\text{Systolic BP}}{\text{Diastolic BP}}$

Systolic: Pressure in major systemic arteries when left ventricle is pumping.

Diastolic: Pressure in major systemic arteries when heart is relaxing.

ie: Aortic valve is closed.

α_1 AR stimulated by on venules will cause flow of blood back to right heart, so There is ↑es venous return. ↑es End diastolic volume, ↑es stroke volume & ↑es CO; so during systole more blood Comes to arteries, so systolic BP↑es.



* when drug A is given systolic is normal & diastolic decrease, so the drug is ↓ing TPR (arteriolodialator)
* when drug B is given systolic is normal & diastolic BP ↑es, the drug is ↑ing T.P.R (arteriloconstrictor)
* when drug C is given diastolic is normal & systolic BP ↑es, the drug is ↑ing Cardiac output.
* when drug D is given diastolic is normal & systolic BP ↑es, the drug is ↓ing Cardiac output.
* when drug F is given systolic is increased, & diastolic is decreased so the drug is ↓ing T.P.R & ↑ing Cardiac output.
* when drug G is given systolic ↓es & diastolic ↑es. so the drug is ↓ing cardiac output & ↑es TPR

Pupilary dialation.

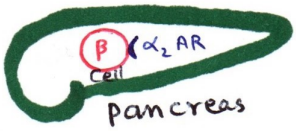
ie: Mydriasis

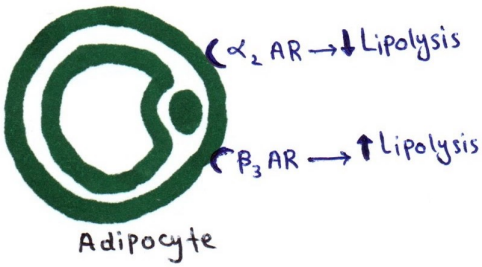
PROSTATE

When prostate increase in size, it constrict urethra, & the male will develope Benign prostatic hypertrophy (BPH).

* To such patients we give drug which dialate prostatic smooth muscle, These drugs are [α_1 Antagonist]
* α_1 blockers are Excellent Anti HTN in BPH patient.
* Taken These drugs may experience Ejaculatory problem

α_1 AR increase Tone of internal urethral sphincter.





β_1 stimulant

- Dopamine
- Dobutamine

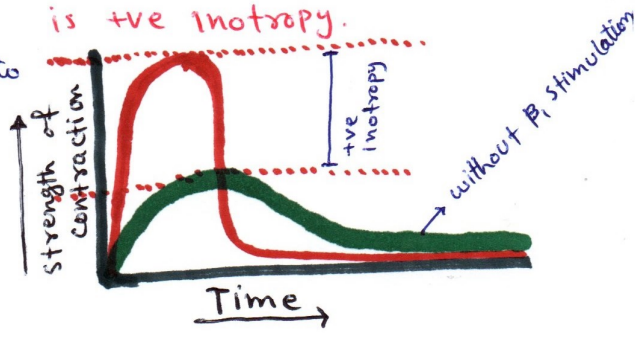
β_1 stimulant are always Cardiostimulant

Bathmotropy: ↑ed Excitibility of specilized conducting system

This ↑es in strength of Contraction is +ve inotropy.

without β_1 stimulate, it takes more time to reach to peak. with β_1 stimulation velocity is Increase, so less time is taken to reach to peak this is +ve clinotropy.

+ve clinotropy ⟶ ↑ed velocity of Contraction.



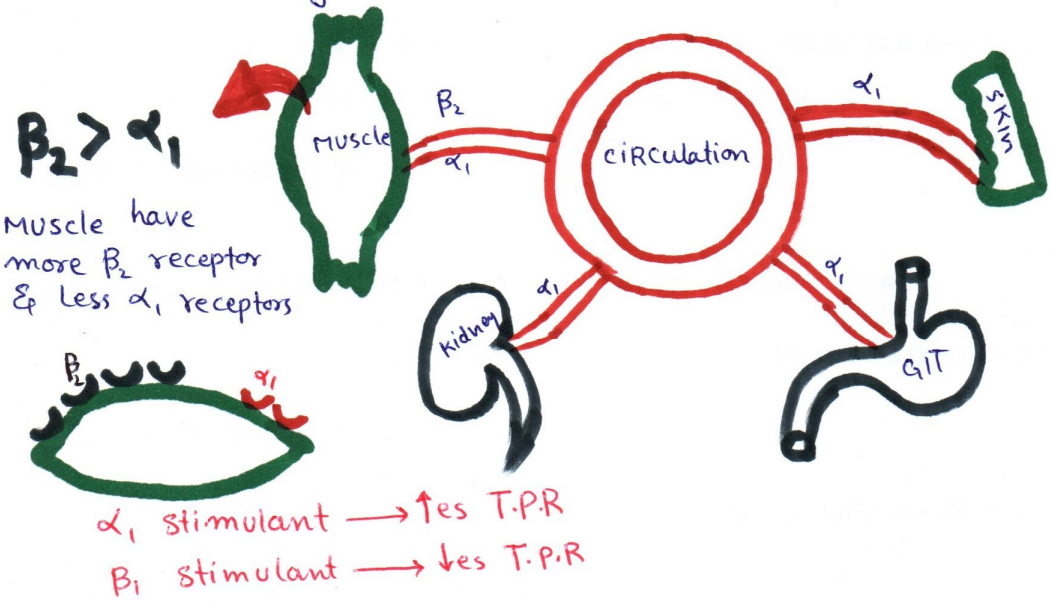
* ↑HR ⟶ +ve chronotropy
* ↑ S.V ⟶ +ve inotropy, +ve clinotropy
* ↑H.R x ↑S.V = ↑CO = ↑ systolic BP

One of typical function of β_1 blocker is to Cardioinhibitor.

β_1-blocker is not only Cardioinhibitor but also inhibit Juxta glomerular Apparatus (JGA) cells & Renin production in the body is decrease, so ↓ Ang II.

* If Angiotensin II mediated vaso constriction is low, than diastolic BP will be less; Ang II mediated veno-constriction will also be less → Venous return will be less → End diastolic volume ↓es → ↓CO → systolic BP ↓es,
* Aldosteron will also be less, so aldosteron mediated salt & water retention is less, so Blood volume is less → venous return ↓es, → CO↓, so systolic BP is less.

So These drugs are used Anti hypertensive drugs, so β_1 blockers ↓es BP by Cardioinhibition; & inhibition of renin Ang, Ald system.



Raynad's disease: There is increased tendency of vasospasticity of distal blood vessele, when expose to cold, vessele constrict so svearly, that person develop cyanosis, & even necrosis in svear Ranyads disease.

* So, Propranolol is contraindicated for patient with perephral blood vessele disease.
* Propranolol should not be given in Asthma patient.

propranolol is contraindicated for patient with insuline dependant Diabetes Melitus (I.D.DM) b/c they have more chance to develop hypoglycemic attack: They develop;

① Anxious look
② palpitation
③ sweating
④ Tremer

→ warning signs

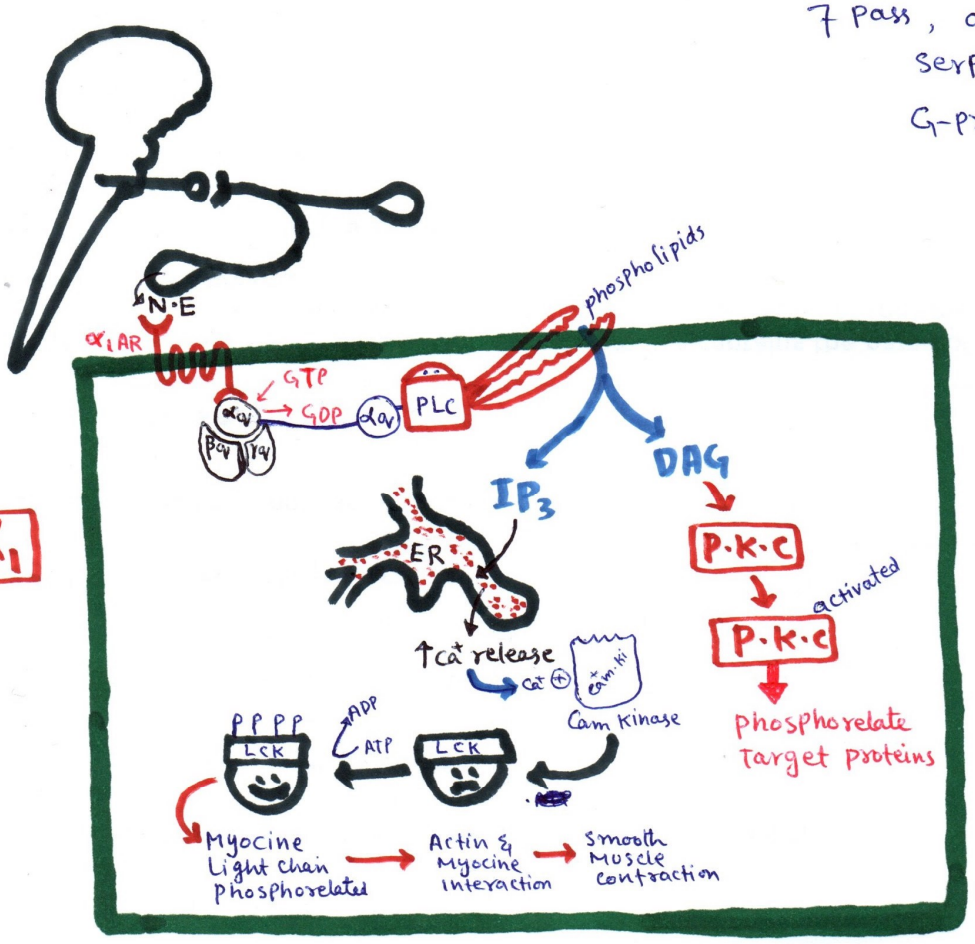
all of these are due to sympathetic overflow.

If β_2-blocker (e.g propranolol) is taken by insulin dependant DM patient & whenever he develop hypoglycemia, he will not develop warning symptoms, so such patient not taking sugar, & also liver will not cause glycogenolysis; so they have more chance to develop life threating hypoglycemia.

* β_2 stimulant have Tokolytic effect on uterus.

Molecular Basis of Adrenergic Drugs & Intracellecular signaling Mechanism:

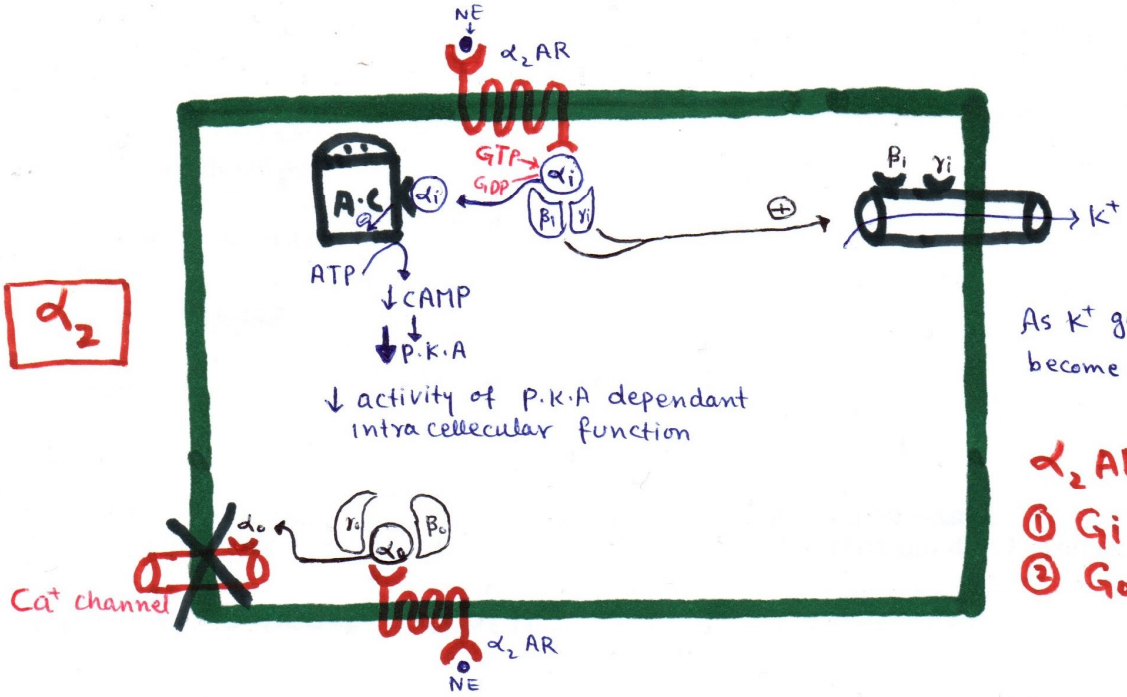
all adrenergic receptors are 7 pass, also called Serpentine OR G-protein coupled receptor.



α_1

Light chain kinase
LCK

DAG act on PKC (protein kinase-c) & just activate them & not phosphorelate them.
the activated P.K.C than posphorelate the target proteins.



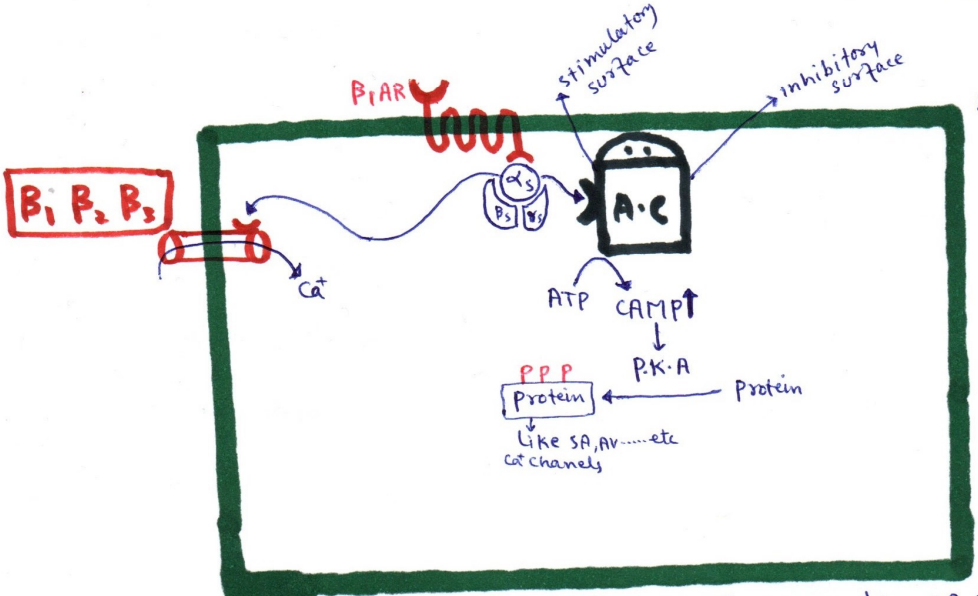
As K^+ goes out cell become hyperpolarized

α_2 AR bind with

1. Gi
2. G_o (G-not)

when α_2 AR bind to α_o, the α_o bind with Ca^+-channel & block them, so no Ca^+ influx occur, This is one way that how α_2 act in presynaptic membrane.

intracellecular mechanism for β_1, β_2 & β_3 are same.



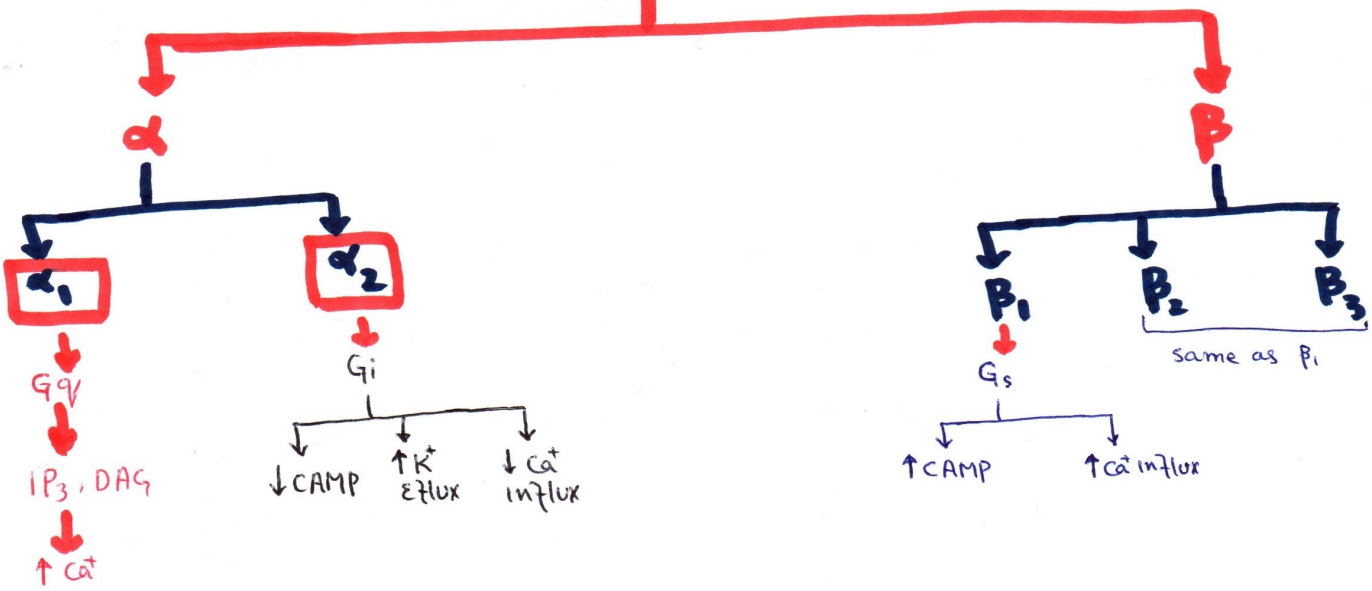
* β_1 stimulation cause Cardiostimulation.

Ca^+-channels are phosphorelate & activated, Ca^+ move in & Ca^+ dependant activity ↑es

α_s Can stimulate Ca^+-channel directly

* suppose Ca^+-channel is present on SA, AV-node, SA & AV-node action potential is Ca^+ dependant, so action potential ↑es.
* Atrial Myocardium ~~α_1~~ activity also depend on Ca^+, so +ve inotropic action.

ADRENERGIC RECEPTORS



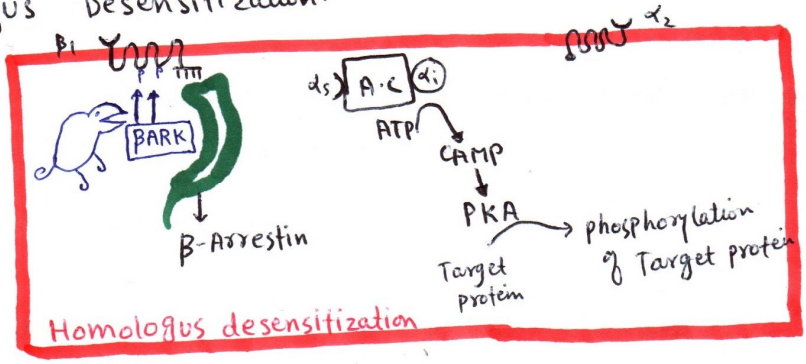
DESENSITIZATION

when agonist act on receptor and giving intracellecular signaling, by time pass the receptor and signaling become less efficient and their responce to agonist decrease.

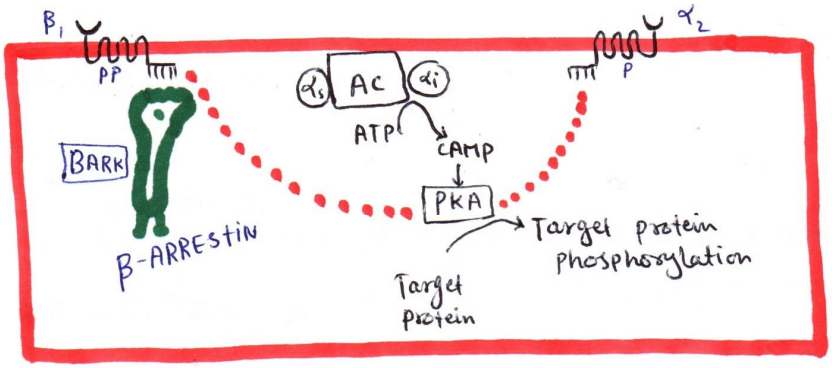
e.g Epi → Receptor → [α unit] —(posphorylation)→ [AC] than action

Receptor has been phosphorylated, when this receptor is phosphorylated, than another protein come & bind with phosphorylated receptor, so α-component does not again bind with receptor, phosphorylation is caused by β-AR kinase (βARK)

In the prescence of this protein β-Arrestin arrest the signaling mechanism, so tissue is desensitized this mechanism is called RAPID DESENSITIZATION, This is an example of Homologus Desensitization.



Rapid desensitization
- Homologus
- Hetrozogus

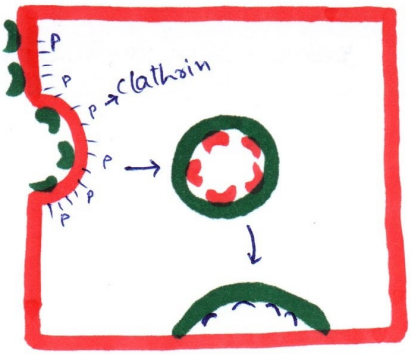


Hetrologus Desensitization

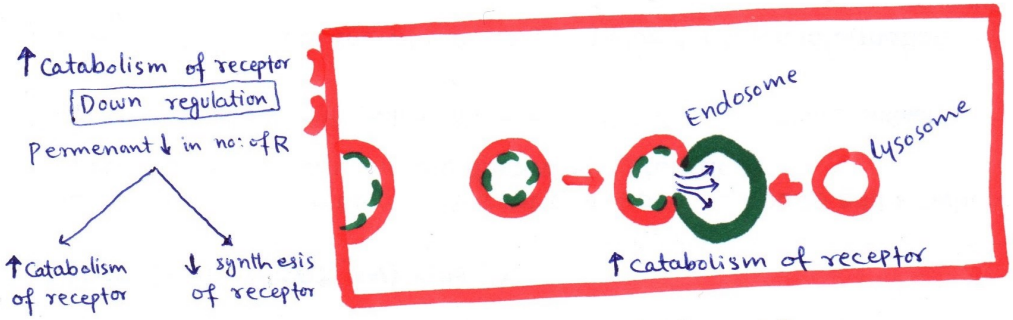
* when agonist act on β_1 it will activate PKA, which cause phosphorylation of many proteins
* if this phosphorylation is caused by α_2 AR, than responce of α_2 to ligand also tes, this type is called Hetrologus Desensitization.

Transiet sequestration

if receptor are too much stimulated than phosphorylated receptor are internalized by clathrin, but after some time they again express on surface & ready for action again. But if stimulation occur too much than receptor will be Catabolized by Endosome.



Down Regulation of Receptor

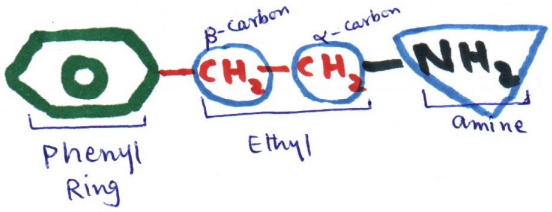


Desensitization

- Rapid desensitization
- Sequestration
- Down Regulation

Structure activity of sympathomimatic Amines

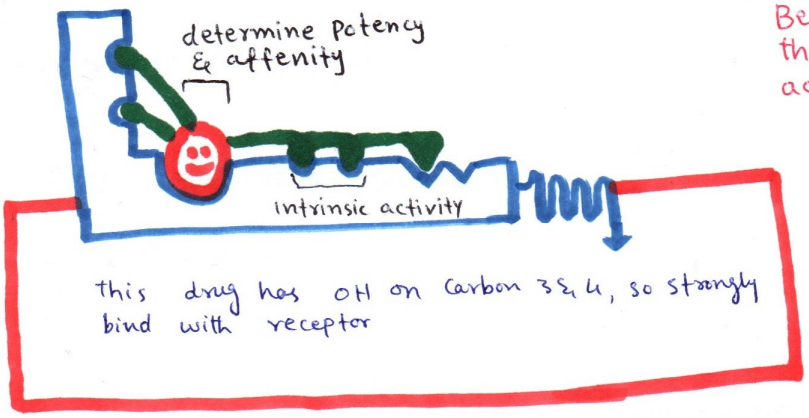
β-Phenyl-Ethyl-Amine
(Parent compound)

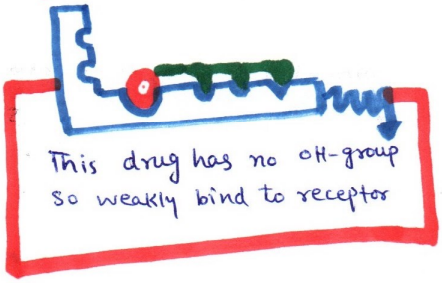


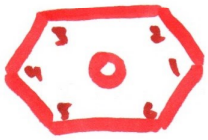
How this structure fit into receptor

For drug to bind with receptor thightly, the drug should be needed to have side chains. So it bind strongly & produce strong stimulation, what are these two side groups?

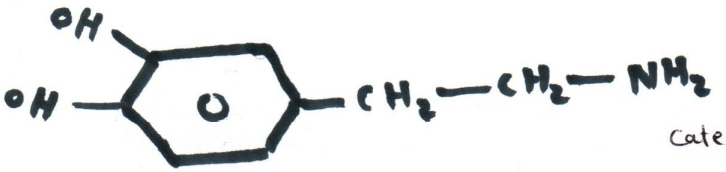
*sympathomimatic drugs should have 2-carbon diffusion B/w Benzene ring & NH_2 group b/c this part determine intrinsic activity of receptor.







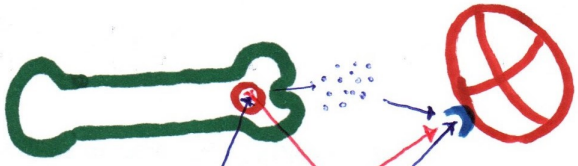
Di OH Benzene ring = catecol ring



Di OH benzene Ethyl amine = catecolamine

Catecolamine
- NE
- Dopamin
- Epineprine
- Iso Pro

NE, Dopamin, Epineprine: natural + Drug
Iso Pro: only drug



① Directly acting drugs directly acts on receptor

② Indirectly drugs act on presynaptic membrane and increase the release of N.E, which than act on receptor.

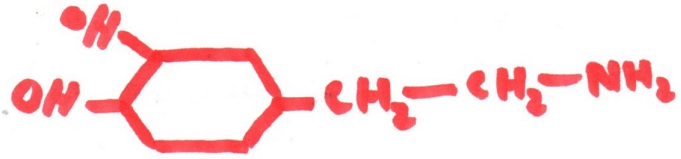
③ Mixed action sympathomimatic drugs, slightly act on direct Adrenergic receptor & slightly act indirectly & ↑ the release of N.E.

All Catecolamine have high potency.

* **Affinity**: ability to bind strong with receptor.
* **Potency**: ability to bind strongly & activate the receptor.

when OH group are removed, the structure become mor lipid soluble

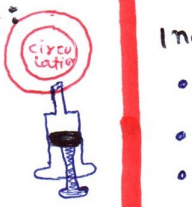
When OH group are removed, now this structure easily enter into nerve ending b/c of lipid solubility & increase the release of N.Epi (Neurotransmiter), such drug are now converted into INDIRECTLY ACTING DRUGS



here on 3 & 4rth Carbon OH are present so it is called Catecholamine

Directly sympathomimatic drugs are:

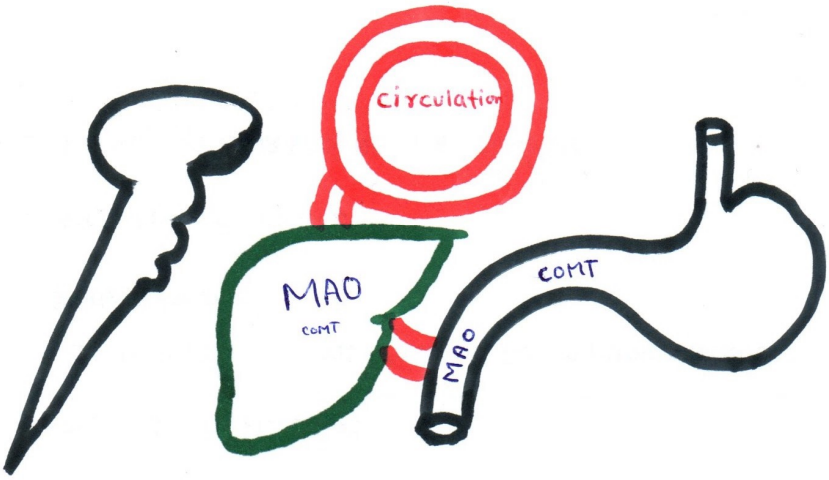
- High Polar Compound.
- They are given parentraly
- has low duration of action.
- not cross BBB b/c of Polarity



here on 3rd & 4rth Carbon, the OH is absent, this is called Noncatecolamine

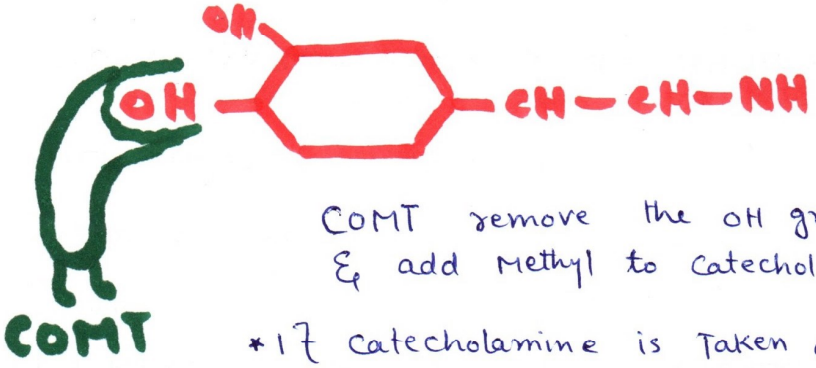
Indirectly sympathomimatic acting drugs are:

- Less polar Compound
- they are given orally
- has high duration of action (resd half life)



If Catecholamine are taken orally, they are not absorbed well b/c they are polar, whatever small amount are absorbed & that is destroyed in GIT by COMT & MAO enzymes.

* Also destroyed by MAO in the liver
* Liver also have small amount of COMT



COMT remove the OH group & add Methyl to Catechol ring.

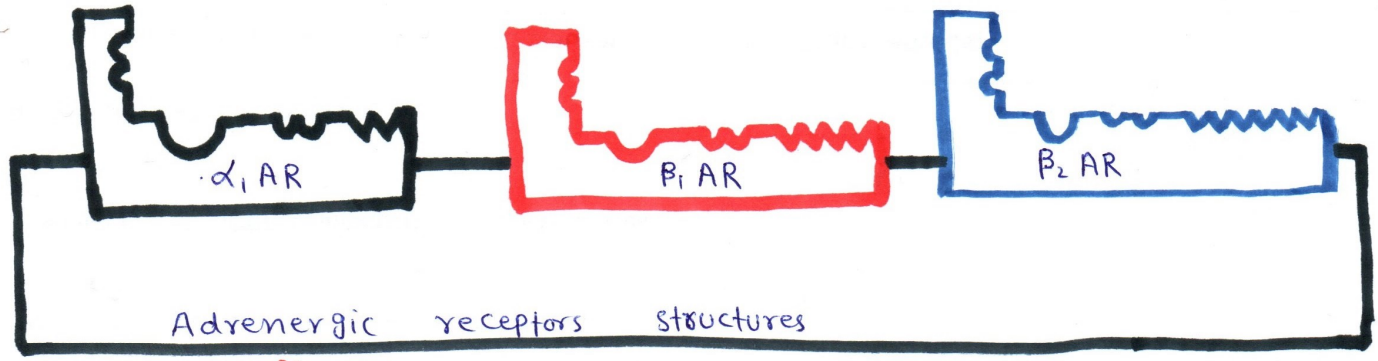
* If Catecholamine is Taken orally its bioavailability is less, so they are Taken parentrally (by injection).

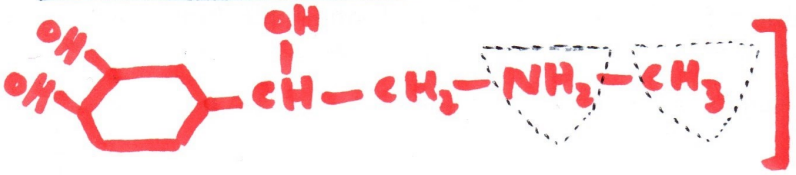
① Ephidrin
② Amphitamine
] Non Catecholamine

These are indirectly acting drug, so they are taken orally. Non-Catecholamine are having longer duration of action b/c they are not taken up by MAO & COMT.

* when Catecholamine are given parentrally they can't cross BBB b/c of lipid solubility, so they don't have direct action on CNS.
* Non-Catecholamine are less polar, and more Lipid soluble so they increase the release of N.Epi.
  - They cross BBB and produce effects and side effects on CNS.

➡ Why different sympathomimatic drug produce different action on different Adrenergic receptor

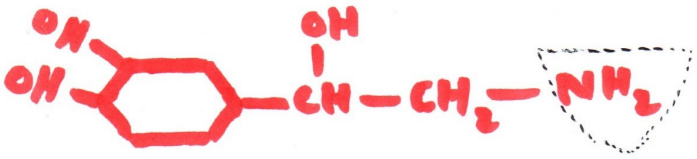




Epinephrine

α_1 | β_1 | β_2

Epinephrine can bind to α_1, β_1, β_2 receptors, due to this action Epinephrine is called **Balanced sympathomimitic drug.**
ie: It act on all adrenergic receptors with almost same affinity.

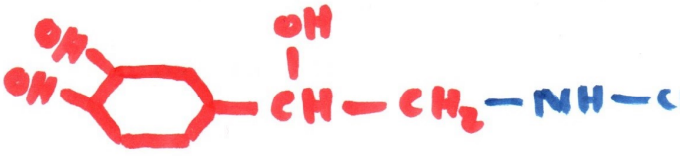


NOR-Epinephrine

α_1 | β_1 | β_2

Norepinephrine has the ability to stimulate α_1 & β_1 Adrenergic receptors but not significantly stimulate the β_2 receptor.

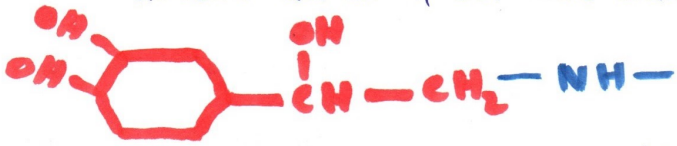
As the amine group group increases the action toward right $\xrightarrow{\alpha_1, \beta_1\ \beta_2}$ les.



Isoproterenol

β_1 | β_2

Its amine group is much higher so do esnit act on α_1 but have action on β_1 & β_2



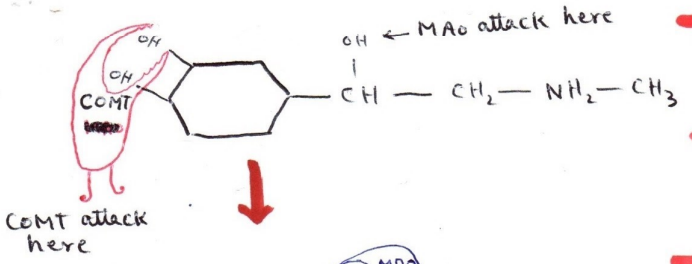
Terbutalin

β_2

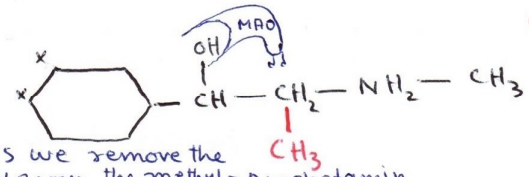
Its amine group are very high, so It canit act on α_1 & β_1 but act on β_2, so best used in Asthma for branchodialation.

Alter the structure of Catecholamine & Make them Non-catecholamine.

① Remove Hydroxyl group from Epinephrine & add Methyl group = Ephedrine



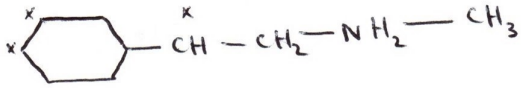
Epinephrine



② As we remove the OH from the methyl = Amphetamin

Ephedrine

- Better absorb orally
- oral bioavailability is more
- Indirectly acting
- Non catecholamine
- Cross BBB & act on CNS
- Due to adding of CH_3 it become more lipid soluble



Amphetamin

It is longer acting

- Become polar
- Cross BBB
- Indirectly acting
- good bioavailability
- Longer duration of action
- Non-catecholamine

End of Adrenergic Agonist
By: Zakirullah Yousufzai

DIRECT-ACTING AGENTS
Albuterol ACCUNEB, PROAIR, VENTOLIN
Arformoterol BROVANA
Clonidine CATAPRES, DURACLON
*Dobutamine** GENERIC ONLY
*Dopamine** GENERIC ONLY
*Epinephrine** ADRENALIN, EPIPEN
Fenoldopam CORLOPAM
Formoterol FORADIL, PERFOROMIST
Guanfacine INTUNIV, TENEX
Indacaterol ARCAPTA
*Isoproterenol** ISUPREL
Metaproterenol GENERIC ONLY
Midodrine GENERIC ONLY
Mirabegron MYRBETRIQ
*Norepinephrine** LEVOPHED
Oxymetazoline AFRIN, VISINE
Phenylephrine NEO-SYNEPHRINE, SUDAFED PE
Salmeterol SEREVENT
Terbutaline GENERIC ONLY
INDIRECT-ACTING AGENTS
Amphetamine ADDERALL
Cocaine GENERIC ONLY
DIRECT AND INDIRECT ACTING (mixed action) AGENTS
Ephedrine AKOVAZ
Pseudoephedrine SUDAFED

Summary of adrenergic agonists. Agents marked with an *asterisk* (*) are catecholamines