Adrenergic System

- Thoraco lumbar outflow.
- pre ganglionic fibres - short.
- NT → ganglia → Ach.
  - organs → Nor adrenaline

Exception → sweat glands (Ach)

Functions → already learned

tyrosine → monohydroxy phenylalanine

phenylalanine
↓ P.A-hydroxylase.
tyrosine → Tyr.
↓ Tyr hydroxylase.
DOPA.
↓ DOPA decarboxylase
DA
↓
NA
↓
NA → reuptake. (major)

dihydroxy phenylalanine - DOPA.
monohydroxy phenylalanine - tyrosine

Dopamine.
↓
DA.
↓ Dopamine β hydroxylase.
NA

DA
- DβH present → Nor adrenaline
- DβH if absent → Dopamine as such

many areas of brain lack DβH, so dopamine remains as such
↓
So NT is dopamine.

- but in sympathetic system, inside vesicles, DβH is present
  ↓
  forms Noradrenaline.

phenylalanine
↓ phenyl alanine hydroxylase.
Tyrosine.
↓ takes up
Tyrosine.
↓ Tyrosine hydroxylase
DOPA
↓ DOPA decarboxylase.
Dopamine.
↓ inside vesicle
DA
↓ Dopamine β hydroxylase
NA

Adrenal gland
D.A
↓ DβH
N.A
↓ N-methyl transferase
adrenaline.

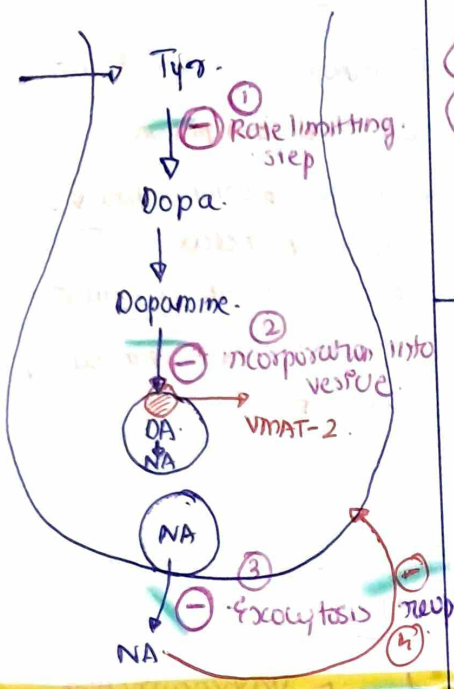
Adrenal gland has DβH and NMT
↓
So Adrenaline is the NT.

☆ Impt difference

① Rate limiting step.
- para
  - ↳ Choline uptake.
- sym.
  - ↳ tyr → DOPA
    - ↳ by tyr hydroxylase.

② termination
para → Ach E - Enzyme degrade
sym → reuptake.

Blockers



① metyrosine.

② Reserpine.

③ Guanethidine

④ Cocaine → ↑ symp. activity

all ↓ sympathetic activity.

Reserpine

- uptake of D.A into vesicle is by VMAT-2.
- ↓
- vesicular monoamine transporter.
- ↓
- It is a non-specific transporter who transports monoamines
- ↓
- Dopamine ✓
- 5-HT / serotonin ✓ also
- Reserpine blocks VMAT-2
- so, N.A & serotonin ↓ both decrease.
- when serotonin ↓ in brain → Depression

- reserpine ↓ NA → ↓ sympathetic.
- ↓ BP.
- Used as Antihypertensive.
- but induces depression.

↓

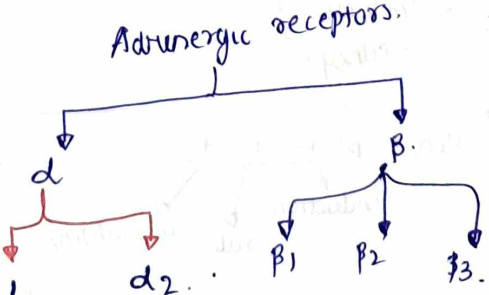
Not Used Now.

Other VMAT-2 inhibitors.

- → Tetrabenazine. — used in huntington's chorea.
- → Deutetrabenazine. — used in huntington's chorea.
- → valbenazine. — Tardive dyskinesia

- huntington's chorea → there is dopamine excess.
- Tardive dyskinesia → side effect of antipsychotic drug

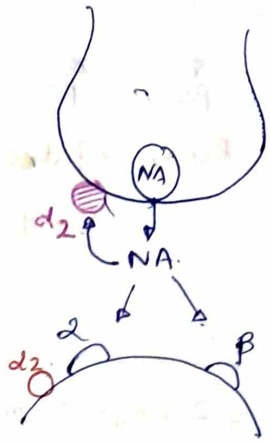
ADRENERGIC RECEPTORS



α1: B Vessel ① vasoconstriction
eye ② mydriasis
prostatic urethra ③ ↓ urine outflow.

In BPH → use α1 blockers

α2 → BRcak. Bagacana.



~~post synaptic receptors~~

α2

- majority is present on pre synaptic membrane.
- when NA binds to pre-syn. α2 → ↓ its release is inhibited.
- α2 act as brake to sympathetic outflow when N.A level ↑
- ⇒ Some α2 are also present post synaptically, they behave just like α1 and cause BP ↓↑ → V.C. mydriasis. urine outflow ↓

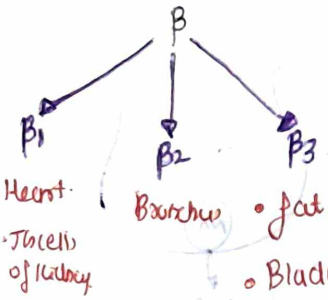
since majority is Brackets

α2

Break to sympathetic

ie, BP ↓, miosis. urine outflow ↑

α1 α2 → same sites but ⊕ & ⊖



Bladder relaxants for overactive bladder.

- adrenergics
- anticholinergics

---

1 heart & 2 lungs. Mnemonic

β_3 → fat → lipolysis.

we tried to find drugs to stimulate β_3 to treat obesity.

↓

we couldn't find that, but on the way we found that β_3 is also in UBladder.

- β_3 – urinary bladder.

↓ urine outflow by relaxing detrusor muscle.

↓

Can be used to treat overactive UB.

DRUGS – β_3 agonist.

"treat overactive bladder" or urinary incontinence.

1. MIRABEGRON (mera)
2. VIBEGRON. (we)

6 ⇒ 3 (β_3)

---

make – mirabegron] adrenergic

bladder – Darifenacin

S – Solifenacin

O – oxybutynin

F – Flavoxate

T – Tolterodine

] anti cholinergic.

Used to treat overactive bladder / urinary incontinence / detrusor muscle instability

---

β_1

- heart (only have in heart).
- JG cells of kidney.

Heart → + + +

- Conduction
- rate
- contractility

- JG cells → release of renin.

↓

renin-AII → ↑ BP

β_2

- Bronchus (2 lungs) Bronchodilation
- GIT → constipation
- Bladder → urine outflow ↓
- Uterus → relax – TOCOLYTIC
- Blood vessel → Vasodilation
- Skeletal muscle → Spindle →
- Liver →

NOTE:

α_1 → vasoconstriction

β_2 → vasodilation

A_1 → C → VC

B_2 → D → VD

See, when symp ↑, both α_1 & β_2 will be activated.

↓

So, will VC or VD occur?

↓

depends on blood vessel ↓

In blood vessel.

If $\alpha_1 > \beta_2$ → VC.

If $\beta_2 > \alpha_1$ → VD.

Sympathetic system does VC & VD depending on site, and does diff. on diff blood vessels.

→ Used in asthma & COPD

effect → to treat preterm labour when contraction comes early / premature

→ tremors. (kayyil വിറയൽ വരുന്നു)

→ When lion വരുന്നു.

↓

ഓടണം.

↓

- Heart (blood venam).
- Skeletal muscle (venam).

SO

↓

vasodilation.

- but Body-il always SL blood ulle indakuu,

↓

what we are actually doing is, oru mosam blood supply kurachit, mattu evide place-ilk kodkkum.

- * skin
- * Internal organs.

] ippo mattenda blood vessels.

- Skin → vasoconstriction
- Internal organs (splanchnic). ⇓ $\alpha_1 > \beta_2$.
- Heart → vasodilation
- Skeletal muscle. ⇓ $\beta_2 > \alpha_1$.

Brain mukyam bigile.

↓

so circle constant.

↓

$\alpha_1 = \beta_2$

↓

(no change)

Sum up.

- Heart, SM → $\beta_2 > \alpha_1$ → VD.
- Skin, Splanchnic → $\alpha_1 > \beta_2$ → VC
- Brain → $\alpha_1 = \beta_2$ → Same.

ADRENERGIC.

Decipher Notes.

1. elderly male – 70y. c/o –
   difficulty in passing urine, poor stream, post void dribbling.
   he had BPH on Examination.
   BP – 160/100.

1. what drug will you prescribe to take care of both BPH & hypertension

2. Explain mechanism of action of drug in this patient

3. what do you understand by "first dose effect of prazosin"?

1. ⇒ Drug → α_1 selective adrenergic Blocker → Prazosin

2. Mechanism OA of Prazosin in treatment of BPH

α_1 adrenergic receptor

location		action
	Blood vessel	→ vasoconstriction.
	Eye	→ Mydriasis.
	prostate Smooth muscle	→ ~~contraction~~ ↑ smooth muscle tone.
	• trigone	→ constriction.
	• prostate	→ tone ↑

↓ urine output

Razosin.

Target receptor → Selective α_1 adrenergic receptor blocker.

BPH

Razosin.
↓
Blocks α-1 receptors
↓
located in prostate, bladderneck, prostatic urethra.
↓
smooth muscle relaxation.
↓
↓ urethral resistance.
↓
↑ urinary flow and relief of BPH voiding symptoms
(hesitancy, dribbling, increased residual urine etc).

Hypertension

Block α_1 receptors.
↓
located on vascular smooth muscles.
↓
vasodilation
↓
↓ peripheral vascular resistance
↓
↓ blood pressure.

(2) First dose effect of Prazosin

Initial dose of prazosin.

↓

Blockade of α_1 adrenergic receptors

↓

vasodilation of peripheral blood vessels

↓

↓ peripheral vascular resistance

↓

Sudden drop in BP

↓

postural hypotension.

The first dose effect of prazosin is a sudden and significant drop in blood pressure (orthostatic hypotension) after the initial dose, causing dizziness / fainting especially when standing due to peripheral vasodilation

→ Only occur in initial doses.

→ later → tolerance → homodynamic due. adjustment

(11) Classify β blockers with one example for each.
Mention therapeutic uses and ADR of PROPRANOLOL?

Uses

(1) hypertension - mild to moderate.

~~hydralazine~~ ~~β~~ receptors.

↓

block N.A.

↓

⇒ on prolong administration

↓

BP gradually falls.

⇒ decrease renin release

⇒ decrease cardiac output

(2) Angina pectoris.

- when taken on a regular basis

↓

↓ frequency of attack &

↑ Exercise tolerance.

⇒ ↓ heart rate & contractility

↓

↓ O_2 demand.

⇒ Beneficial for stable angina.

(3) Arrhythmia

like atrial fibrillation & supraventricular tachycardia.

block β receptor of heart → help regulate rhythm

→ prevent abnormal electric impulse.

adverse effects

1. CNS
- Bradycardia
- hypotension
- Heart block — contraindicated.
- worsening heart failure.
- Rebound hypertension
  withdrawal after chronic use. should be gradual.

2. Respiratory
- worsening of asthma & COPD — contraindicated.

3. CNS
- fatigue, lethargy.
- dizziness.
- depression.

4. metabolic effects.
- Hypoglycemia.
- masking of hypoglycemia symptoms

5. GI
- Nausea, vomiting
- upset.

peripheral vascular effect
- cold extremities due to peripheral vasoconstriction. (β_2 block).

Contra → partial/complete block, Asthma, COPD, diabetes.

Contraindications of β blocks
- Asthma, COPD
- people having bradycardia
- Heart block — due to ↓ in conduction through A-V node.
- severe hypotension patient
- acute heart failure
- pheochromocytoma
- severe peripheral arterial disease

Prazosin.
- D highly selective α_1 adrenergic receptor antagonist.

MOA
- prazosin selectively block α_1 receptors → ⊖ NA binding
- ↓ causes vasodilation
- miosis
- ↑ vein flow.

PK
- absorption — orally well absorbed
- B.A — 70%
- onset - 1-3 hr
- Dur — 6-12 h
- metabolism - liver
- Excretion - bile.

Indications

- hypertension ✓
- BPH. ✓
- Raynaud's phenomenon.

ADR

- first dose effect ★
- Nasal congestion
- dizziness, fatigue.

Contraindication

- hypotension
- ~~BPH~~.

Precautions

- hypotensive patient
- first dose - mm.
- bed time.

Carvedilol

- Non-selective β adrenergic blocker with α_1 blocking activity
- ie, $\beta_1 + \beta_2 + \alpha_1$
- It is also a calcium channel blocker. ★

MoA

- Block β_1, β_2 α_1 receptors.
- (-) binding of N.A.

PK

- absorption - orally - ww
- B.A - 30% - high FPM
- metabolism - CYP2D6.
- protein binding >98%
- excretion - bile.

Indications

- Hypertension - to reduce bp.
- chronic heart failure → specifically employed cardioprotective in CHF
- LV dysfunction.
- Angina pectoris

ADR

- hypotension - orthostatic
- Bronchospasm.
- Bradycardia.
- mask hyperglycemia symptoms.

Contra.

- sever hypotension
- Asthma
- hypersensitivity.

Precautions

- Diabetics
- rebound angina. ★

Dopamine

Dopamine in Cardiogenic shock Reason)
- ↑ C.O
- ↑ renal perfusion.
- ↑ stability to BP.

- Central NT
- D_1, β_1, α_1
- NT – involved in regulation of movement.
- ↑ SBP
  no effect on DBP.

Actions

0.5 – 2 ug/kg/mt → Acts on D_1 receptor
- ↑ renal, mesenteric & coronary blood flow.
- Natriuresis, Diuresis.
- prevents renal shutdown in cardiogenic shock.

2–10 ug/kg/mt – acts on D_1 β_1
- ↑ BP. (+) Inotropic.
- ↑ blood flow to renal organs.
- no chronotropy.

10 – 20 ug/kg/mt – act on α_1
- vasoconstriction, increase BP.
- ↓ blood flow to vital organs.

Therapeutic use
- Severe CCF – Cardiogenic shock
- Severely ill patients with chronic heart d/s or renal failure.
- Improve cardiac & renal function

prep – 20/40 mg per ml.
mixed in 200ml of 5% dextrose.
- 8–16 drops/minute

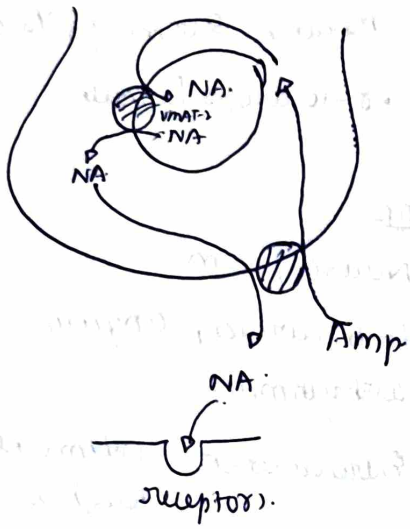
ADR
- Nausea, vom.
- tachycardia, angina, arrhythmias.
- Extravasation – ischemic necrosis/ sloughing.

Precautions
in shock – hypovolemia should be corrected by use by blood transfusion, plasma or fluids.

Amphetamine

- synthetic cmpds.

MOA
- release NA from adrenergic neurons.
- enters through NET, DAT, VMAT-2.
- displaces NA from vesicles through exchange diffusion.
- reverse transport through NET, DAT.



ACTIONS

CNS → alertness,

- ↑ conc & self confidence.
- delays onset of fatigue.
- Improves physical performance.
- produce wakefulness.
- postpone sleep.

Short lived actions: Counter productive

- CVS → cardiac (+)
- Smooth → control sphincter muscle
- respiratory ↑
- suppress apetite

Transmitters

NE - alertness & anorectic.

DA → locomotor action

Serotonin → disturbance of perception

- long term use: Tolerance, dependence.
- Included in DOPE test

ADR

CNS - delirium, psychosis

CVS - tachycardia, palpitation, angina

dry mouth - metallic taste, Nausea, vom.

Urinary retention.

Clinical

- Analogue - Drug of abuse.
- ADHD
- Narcolepsy

X——————X

Nasal decongestants

- Drugs that produce vasoconstriction of Nasal mucosa
- relieve nasal block.

use - ↓ associated with cold, sinusitis

ADR

- Initial stinging.
- Impaired mucociliary clearance
- Anosmia
- prolonged use - hypertension.
- Sudden stop - rebound Congestion.

Topical	Oral
• Imidazoline.	• Ephedrine
• Naphazoline.	• pseudo ephedrine
• Oxymetazoline.	• phenyl ephrine
• 0.05 - 0.1% solution.	• short DOA.
• Long DOA - 12h.	

• Use of.

β blockers.

- Non-selective.
  - without ISA → propranolol, Timolol.
  - with ISA → pindolol
  - with α blocking ppty. → Labetalol.
- Cardioselective
  - Metoprolol
  - Atenolol.
  - Bisoprolol.
  - Esmolol.
  - Betaxolol.

β blockers

- 1st gen (nonselective)
  - propranolol.
  - Timolol
  - pindolol.
- 2nd gen (β1 or cardio selective)
  - Metoprolol.
  - Atenolol.
  - Esmolol.
  - Bisoprolol.
- Third gen (with α blocking)
  - Betaxolol.
  - Nebivolol.

---

④ MI

- to reduce risk of further attacks
- by reducing O_2 demand.
- reduces mortality

⑤ ~~Congestive heart failure.~~

⑥ Migraine prophylaxis

- effective in preventing migraine.

⑥ Thyrotoxicosis

Controls → tremor, palpitation etc.

⑦ Essential tremors

first-line

⑧ Anxiety.

blood - tremor palpitation

⑨ Hypertrophic cardiomyopathy