

CHARACTERISTICS AND CHEMISTRY OF Adr. AGONIST

- Most are derivatives of B-phenylethylamine
- Subst on benzene ring or ethylamine side
- Two key features of these drugs are:
 - No. & location of OH
 - Nature of subst. on amino nitrogen

Variety of compound
 For α-recep. B-recep
 ability to penetrate CNS.

• Catecholamine: syns. from Tyrosine (Non ex. A.A), derived from dietary source or phenylalanine E.A.A

CATECHOLAMINE

- Contain 3,4 dihydroxy benzene gp (Side by side - ortho)

★ Drugs: NOT orally. Exo = ID
 ENDOGENOUS = END

- epineph
- Nor-epineph
- dopamine
- Isoprenaline
- Dobutamine

Properties

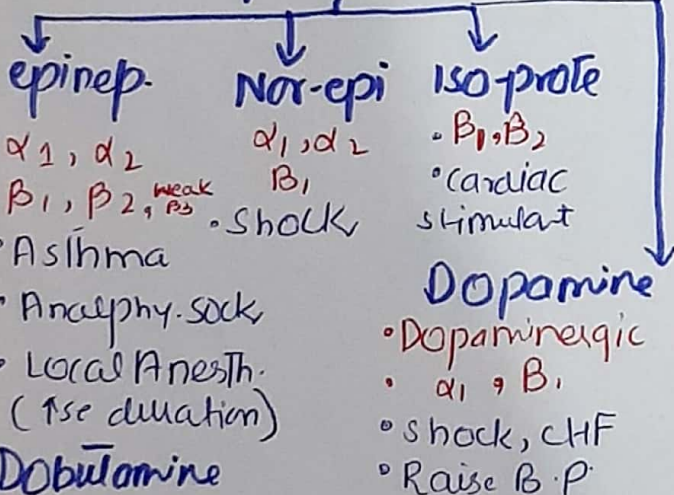
- ★ High potency: due to 3,4-OH group
- ★ Rapid Inactivation

MAO: intra-neuronally, Gut wall, Liver (orally → inactive)
 Parent → short-life.

COMT: post-synap, Gut wall

- ★ Poor penetrat. in CNS = Due to polarity

Receptor & uses



NON-CATECHOLAMINE

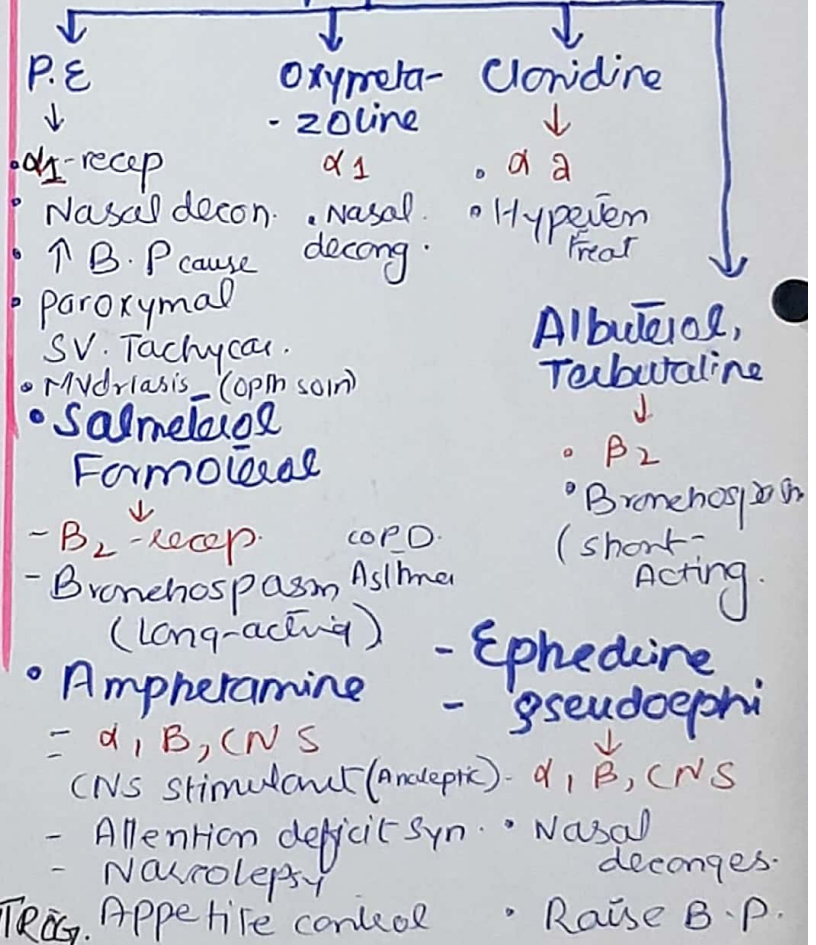
- Lack -OH groups
- Long t_{1/2}
- As NOT inactivated by COMT, poor substrate for MAO.

Drugs: Long duration TEA & Phenylephrine

- Phenylephrine
- Ephedrine
- Amphetamine
- Salbutamol
- Tyramine

↓ OH group = ↓ polarity = ↑ CNS Penetration

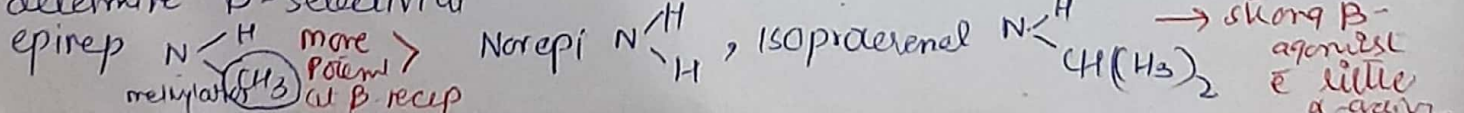
Recep & uses



Albuterol, Terbutaline
 ↓
 • β₂
 • Bronchospasm (short-acting)

SUBSTITUTION ON AMINE NITROGEN

- determine β-selectivity



DIRECT-ACTING ADRENEGIC AGONIST

Binds to adrenergic receptor on effector organ, not interacting with pre-synaptic neuron. — used widely.

EPINEPHRINE / ADRENALINE

Norepinephrine / adren. α -receptor affected most

ACTIONS

Vasoconstriction

- $\uparrow$ PVR
- $\uparrow$ se (sys. & diaz. B.P.) more than epi due to only α -effect
- weak β_2 -effect

Baroreceptor Reflex

- $\downarrow$ NE $\rightarrow$ $\uparrow$ PVR
- $\downarrow$ vagal activity
- reflex bradycardia ($\downarrow$ HR)
- $\rightarrow$ Tachycardia.

Barorecep. reflex: homeostatic mechanism for preventing abnormal $\uparrow$ se in B.P.

Treatment of shock $\rightarrow$ as it $\uparrow$ se B.P.

ACTIONS

mnemonic at back

CVS

- major effect (Tachycardia)
- $\uparrow$ ion. + chronotro. β_1
- CO $\uparrow \rightarrow \uparrow$ O₂ demand (ABP) on myocard.
- Activate β_1 on kidney
- Renin release
- Ag-II $\rightarrow$ vasoconstrict

Respir.

- Bronchodilation (B₂) A-shock
- Inhibit Histamine release
- Hyperglycemia
- B₂ $\rightarrow$ glycogenolysis Δ Diabetic PI
- Glucagon release
- $\alpha_2 \rightarrow \downarrow$ insulin release

* Kinetics:-

- IV — rapid onset
- Dura — 1-2 min
- COMT, MAO — metabo.
- excrete inactive metabolite $\rightarrow$ urine.

ADRS

- similar to epi
- vasoconstrictor
- blanching & sloughing of skin along infec. vein
- Tissue Necrosis = Extravasation
- NOT to adm in peripheral vein
- Antidote = phentolamine (α -blocker)

* Ther. use:- In cardiac arrest (Restore rhythms)

- Anesthetic: Local Anesthetic
- Also Applied [1:100,000 parts of epin] Topically
- $\rightarrow$ control oozing capillary Blood.

Kinetics:-

- Rapid onset, $\downarrow$ duration
- IM > IV, s/c, ET & Inhalation. metab. rapidly by
- Metabolite metanepi & vanillyl mandelic acid $\rightarrow$ urine.

ADRS:-

- Anxiety, Fear, Tension, Headache, Tremor
- cardiac arrhy. (Ecdigoxin), pulm. edema, $\downarrow$ dose in hyperthyroid

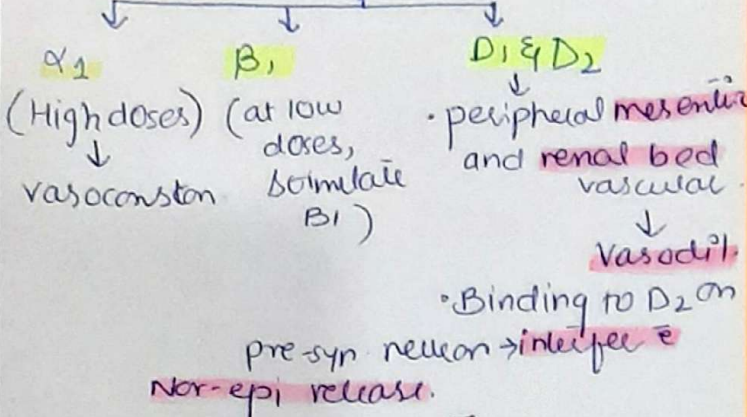
Adrenaline orally inactive = due to COMT & MAO

HT $\rightarrow$ Hypothyroid Angina

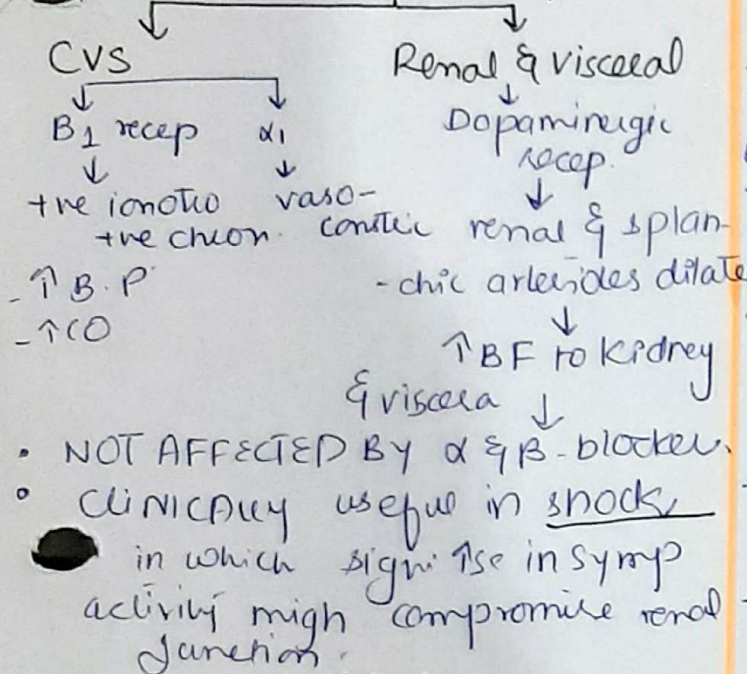
DOPAMINE

use other than digoxin^{MAO on blue table}
 → the ionotropic → **DOBUTAMINE**
 NO Action on **D1/D2**

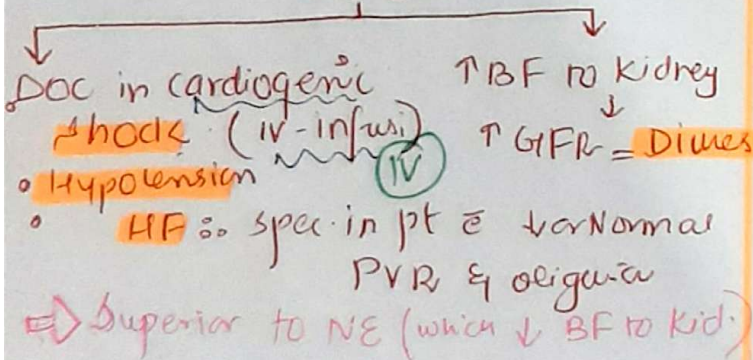
- Metabolic precursor of Nor-epi
- Occur in CNS, basal ganglia, Adrenal medulla



ACTIONS & Therap. uses.



USES



ADR: Overdose same as $\uparrow$ symp. stimula.

- N/HT / arrhythmias
- ADRs are short-lived due to rapid metab by COMT or MAO.

- Synthetic direct-acting catecholamine — β_1 agonist
- $\uparrow$ HR • $\uparrow$ CO • few vascular effects
- use to $\uparrow$ CO in **Acute HF** **IV**
- For ionotropic support after cardiac surgery
- **$\uparrow$ CO BUT DON'T $\uparrow$ O_2 myocard. demand**
- " A MAJOR ADVAN over other symp-mimetic drugs
- **$\uparrow$ AV conduction** — use & caution in atrial fibrillation
- Tolerance develops & prolong use.
- ADRs similar to epinep.

*- PHENYLEPHRINE

Synthetic, direct acting → α_1 receptor agonist

* vasoconstriction → $\uparrow$ systolic $\uparrow$ diastolic B.P

- Induce reflex bradycardia, when given parenterally.
- Otherwise NO effect on heart

CLINICAL USES:-

- Treat **Hypoten** in hospit. pt & surgical pts (& rapid HR).
- Topically → **Nasal deconges** ^{most imp}
- In opth. sch → **Mydriasis** ^{when cyclopleg NOT}
- Replaced pseudoeph. since it was misused to make methamphetamine

ADR = Large dose = • Hypertensive Headache
 • Cardiac irregularities
 • β -agonist = like dop & dobu = acute HF
 • β -blocker = chronic & stable HF

Isoproterenol

- Direct acting - synthetic
- β_1 & β_2 — Non-selectively (DRAWBACK).
- α -recept. effect — Insignif.
- $\uparrow$ HR, $\uparrow$ Contractility, $\uparrow$ CO
- Dilate arterioles $\rightarrow \downarrow$ PVR (β_2)
- Bronchodilator (β_2)
- Only useful in AV block
- ADR similar to epineph.
- Active as epineph.

ALBUTEROL & Terbutaline

- Short acting - β_2 -agonist
- Bronchodilator (given via MDI)
- DOC in acute Asthma*
- When adm orally $\rightarrow$ Tachycardia or arrhythmias due to β_1 -activation
- CI MAO inhibitor, [CV-risk] Prevent labor
- Off-label - uterine relaxant - premature labor
- ONSET Terbutal > Albuterol
- ADR = Tremors, restlessness, apprehension & anxiety

OXYMETAZOLINE

- D. Acting, Synthetic, α_1 & α_2
- In OTC short-term nasal decongest; Ophthalm. drop (for redness of eyes assoc. w/ swimming, colds, contact lenses $\downarrow$ congestion)
- Cause vasoconstrict $\rightarrow$
- Rebound congestion & dependence, nervousness, Headache, Trouble sleeping
- Local irritation & sneezing (Intra-Nasal Adm)
- Abs. in systemic circ. regardless of route of adm.

α_{1a} = UT

α_{1b} = blood vessel.

FENOLDOPAM

- agonist of peripheral D_1 recep.
- Rapid acting vasodil. $\rightarrow$ Treat HT
- Act on coronary, kidney & mesenteric arteries
- R-isomer is active of racemic mixture
- Extensive 1st-pass metabolism $t_{1/2} = 10$ min after IV
- Headache, flushing, dizziness, N/V/Tachycardia (due to vasodilation)

Treat severe HT

SALMETEROL & Formoterol

- long-acting β_2 -agonist (LABA) (selective)
- Single dose via = BronchoDilation dry powder inhaler, over 12 hrs
- albuterol = 3 hr
- Salmeterol = somewhat delayed onset
- Formoterol = Rapid onset
- effective/recomm. in comb. w/ corticosteroids
- DOC — Nocturnal Asthma*
- $\uparrow$ risk of Asthma-related deaths

CLONIDINE: - α_2 -agonist

- Treat Hypertension (when 2 or more drugs could not produce response)
- Action of central pre-symp α_2 -recept $\rightarrow$ inhibit vasomotor centre $\downarrow$ Symp. outflow to periphery $\downarrow$ B.P.
- $\downarrow$ Symp. asso. w/ opiates, Tobacco, & benzodiazep. withdrawal

ADR: Lethargy, sedation, constip. & Xerostomia (like anticholin.)

Rebound Hypertension (if Abrupt discontin.)

Doesn't affect RBF & GFR so can be used in HT due to renal disease

MIRABEGRON = β_3 agonist

- Relax detrusor muscle = $\uparrow$ bladder capacity
- $\uparrow$ B.P.
- $\uparrow$ Level of digoxin (for overactive bladder)
- Inhibit CYP2D6 isozyme = $\uparrow$ metabolic effect and other things etc.

INDIRECT-ACTING AGONIST

- Causes release, inhibit re-uptake, inhibit degradation of epi & NE
- potentiate the effect
- Don't Act on post-syn recep.

(CAT)

Amphetamine

- CNS-stimulant (analeptic)
- Abusive potential ^{even in 2-3 doses = addiction}
- ↑ B.P. (α_1)
- Cardiac stimulation (β_1)
- ↑ se NON-VESICULAR release of catecholamine (epi & dopa) from nerve terminals.
- cross BBB.

★ Modafinil (brand)

- For excretion = make urine acidic by NH₄Cl
- ONLY drug in dop test of Athlete

TYRAMINE

- ↓
- NOT useful clinically
- found in fermented food
 - aged cheese
 - chianti wine
- By-product of Tyrosine metab.
- metab. by MAO
- If MAO inhibi → vasoconstrictor epi occurs

COCAINE

- unique among LOCAL ANESTHETICS
- Block Na⁺/Cl⁻ depolar
- Nor-epi transporter (req. for cellular re-up)
- Thus potential effect of epi & Nor-epi
- ↑ B.P. (α_1)
- ↑ stimulation (β)
- Drug of abuse.

MIXED-ACTION AGONISTS (ephedrine & pseudoephedrine)

- release stored Nor-epi from nerve terminal
- stimulate α & β recep.
- are NOT CATECHOL → poor substrate for COMT & MAO
- long duration
- excell absor.
- CNS penetrate
- Incomp metab of pseudo
- unchange elim of eph.

EPHEDRINE

- **vasocons** → ↑ sys. & dia. B.P. Treat Hypoten
- Cardiac stim.
- **Bronchodil** - BUT less potent & slower acting than epi & iso pro.
- mild CNS-stimulant → ↑ alertness, ↓ fatigue, ↓ sleep.
- ↑ athletic performance.
- ITS Herbal supp → BANNED BY FDA. (CV-reactions)

PSEUDOEPHEDRINE

- Primarily use to treat nasal & sinus congestion.
- use illegally to produce Methamphetamine (CNS-stimulant, recreational drug)
- 2nd line agent for ADHD & Obesity

COMMON ADES of Adrenergic Agonists:-

- 1) Arrhythmias
- 2) Headache
- 3) Hyperactivity
- 4) Insomnia
- 5) Nausea
- 6) Tremors