CHARACTERISTICS AND CHEMISTRY OF Adr. AGONIST

- Most 're derivatives of B-phenylethylamine
- subst on benzene ring or ethylamine side < variety of compound → For α-recep. B-recep; ability to penetrate CNS.
- Two imp features of these drugs are.
  (1) No. & location of OH
  (2) Nature of subs. on amino nitrogen

- Catecholamine: syns. from Tyrosine (Non e/s A.A), derived from dietary source or phenylalanine E.A.A

CATECHOLAMINE

- Contain 3,4 dihydroxybenzene gp (side by side -OH)

★ Drugs: • NOT orally. EXO = ID, ENDOgenous = END
1) epineph (2) Nor-epineph
(3) dopamine (4) Isoproterenol (5) Dobutamine.

Properties

*) High potency: due to 3,4-OH group

*) Rapid Inactivation

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

COMT: post-synap, GUT wall

*- poor penetrat. in CNS = Due to polarity

Receptor & uses

epinep.
- α_1, α_2
- β_1, β_2, weak β_3
- Asthma
- Anaphy. sock
- Local Anesth. (↑se duration)

Nor-epi
- α_1, α_2
- B_1
- Shock

Iso-prote
- B_1, B_2
- cardiac stimulat

Dopamine
- Dopaminergic
- α_1, B_1
- shock, CHF
- Raise B.P

Dobutamine
- B_1
- acute HF

NON-CATECHOLAMINE.

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

Drugs: • Long duration TEAS + Phenylephrine
1) Phenylephrine (2) Ephedrine — oral + Inhalat
3) Amphetamin. 4) Salbutamol (5) Tyramine

↓OH groups = ↓ polarity = ↑CNS penetration

Recep & uses

P.E
- α_1-recep
- Nasal decon.
- ↑B.P cause
- paroxymal SV. Tachycar.
- Mydriasis (opth soln)

Oxymeta-zoline
- α_1
- Nasal decong.

Clonidine
- α_2
- Hyperten treat

Albuterol, Terbutaline
- β_2
- Bronchospasm (short-Acting.

Salmeterol, Formoterol
- B_2-recep. COPD
- Bronchospasm Asthma (Long-acting)

Amphetamine
- α, B, CNS
- CNS stimulant (Analeptic)
- Attention deficit Syn.
- Narcolepsy
- Appetite control

- Ephedrine - Pseudoephi
- α, B, CNS
- Nasal decongest.
- Raise B.P.

SUBSTITUTION ON AMINE NITROG.

- determine B-selectivity

epinep $N<^{H}_{CH_3}$ (methylated) more potent > at B recep; Norepi $N<^{H}_{H}$, Isoproterenol $N<^{H}_{CH(CH_3)_2}$ → strong B-agonist & little α-activity

DIRECT-ACTING ADRENERGIC AGONIST

Binds to adrenergic receptor on effector organ, without interacting with pre-synaptic neuron — used widely.

EPINEPHRINE/ADRENALINE

In adrenal gland chromaffin cell

NE → methylated → Epi → (Epi + NE both stored) ← on stimulation releases

epineph 80% — 20% NE

- β-blockers → (+ve) → α; β
- At high doses vasoconstric → ↑B.P, ↑PVR
- At low doses vasodil
- β-blockers → β → (-ve)

ACTIONS

(mnemonic at back)

CVS

- major effect (Tachycardia)
- +ve ion. + chronotro. β_1
- CO ↑ (↑BP) → ↑O_2 demand on myocar.
- Activate β_1 on kidney → Renin release → Ag-II → vasoconsi
- α_1-effect → vasoconstric (skin, mucus, viscera)
- β_2-effect → vasodil (liver, sk. mus)
- cumulative effect: ↑se systolic B.P
  - slight ↓se Diastolic B.P

Respir.

- Bronchodila — DOC in acute Asthma (β_2), A-shock
- Inhibit Histamin release — Type I HS. rex
- Hyperglycemia
  - β_2 → glycogenolysis, Glucagon release — △ Diabetic Pt.
  - α_2 → ↓ insulin releas.
- Lipolysis (β_1-) β_2 (more), β_3 main → ↑se cAMP → ↑ Hormone sensitive lipase → Hydrolysis of TG → FA, Glycerol

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

- Anesthetic: Local Anesthetic [1:100,00 parts of epin] vasoconstric
  - Also applied topically → control oozing capillary Blood.

Adrenaline Orally inactive = due to COMT & MAO

Kinectics:- rapid onset, ↓ duration
- IM > IV, S/C, ET & inhalation. metab. rapidly by MAO & COMT
- metabolite metanepi & vanilly mandelic acid → urine.

ADRs:- Anxiety, Fear, Tension, Headache, Tremor, cardiac arry. (ē digoxin), pulm. edema, ↓dose in Hyperthyroid

CI ← HT, Hyp. thyroid, Angina

Norepinephrine / Nor-adren.

α-receptor affected most

when given in Therapeutic dose →

ACTIONS

Vasoconstriction

- ↑PVR
- ↑se (sys. & dias. B.P) more than epi due to only α-effect
- weak β_2-effect
  - ↓
  - [Treatment of shock → as it ↑se B.P.]

Baroreceptor Reflex

- ↑NE → ↑PVR → ↑vagal activity → reflex bradycardia (↓HR)
- 1st Atropine (-) → Tachycardia.

Baroreceptor reflex: homeostatic mechan. for preventing abnormal ↑se in B.P

★ - Kinectics:-
- IV — rapid onset
- Dura — 1-2 min
- COMT, MAO — metabo.
- excre inactive metabolite → urine.

ADRS

- similar to epi
- vasoconstrictor → blanching & sloughing of skin along injec. vein
- Tissue Necrosis ≡ Extravasati
- NOT to adm in Peripheral vein
- Antidote = phentolamine (α-blocker)

DOPAMINE → use other than digoxin → +ve ionotropic ← DOBUTAMINE (MoA on B1 side; NO Action on D1/D2)

Dopamine

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

Receptors

- α_1 (High doses) → vasoconstn
- B_1 (at low doses, stimulate B1)
- D_1 & D_2 → peripheral mesenteric and renal bed vascular → Vasodil.
  - Binding to D_2 on pre-syn neuron → interfere ē Nor-epi release.

ACTIONS & Therap. uses.

- CVS
  - B_1 recep → +ve ionotro, +ve chron
  - α_1 → vaso-constric
  - ↑ B.P
  - ↑ CO
- Renal & visceral → Dopaminergic recep → renal & splanchnic arterioles dilate → ↑ BF to kidney & viscera
- NOT AFFECTED BY α & B-blocker.
- Clinically useful in shock, in which sign. ↑se in symp activity might compromise renal function.

USES

- DOC in cardiogenic shock (IV-infusi) (IV)
- ↑ BF to kidney → ↑ GFR = Diuresis
- Hypotension
- HF ∴ spec. in pt ē ↓ or Normal PVR & oliguria
- ⇒ Superior to NE (which ↓ BF to kid.)

ADR: Overdose same as ↑ symp. stimula.
- N/HT / arrhythmias
- ADRs are short lived due to rapid metab by COMT or MAO.

Dobutamine

- Synthetic direct acting catecholamine — B_1 agonist
- ↑se HR. ↑ CO. few vascular effects
- Use to ↑se CO in Acute HF (IV)
- For ionotropic support after cardiac surgery
- ↑ CO BUT DON'T ↑se O_2 myocar. demand
  " A MAJOR ADVAN over other symp.mimetic drugs
- ↑se AV conduction — use ē caution in atrial fibrillation
- Tolerance develop ē prolong use
- ADRs similar to epinep.

★- PHENYLEPHRINE

Synthetic, direct acting → α_1 recept agonist

★ vasoconstr. → ↑ systolic, ↑ Diastolic B.P

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

CLINICAL USES :-

- Treat Hypoten. in hospit. pt & surgical pts (ē rapid HR).
- Topically or orally → Nasal deconges. (most imp)
- In oph. soln → Mydriasis when cycloplg NOT req.
- replaced pseudoephe. since it was misused to make methamphetamine

ADR = Large dose = • Hypertensive Headache • Cardiac irregul.

∴ B-agonist = like dop & dobu = acute HF
B-blocker = chronic & stable HF

① Isoproterenol
- Direct acting - synthetic
- β_1 & β_2 — Non-selectively (DRAWBACK).
- α-rece effect — Insignif.
- ↑ HR, ↑ Contractility, ↑ CO
- Dilate arterioles → ↓ PVR (β_2)
- Bronchodilator (β_2)
- Only useful in AV block
- ADR similar to epineph.
- Active as epineph.

FENOLDOPAM
- agonist of peripheral D1 recep.
- Rapid acting vasodil. → Treat HT
- Act on coronary, kidney & mesenteric arteries
- R-isomer is active of racemic mixture
- Extensive 1st-pass meta.
- $t_{1/2}$ = 10 min after IV
- Headache, flushing, dizziness, N/V / Tachycardia (due to vasodilation)
- Treat sever HT

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

SALMETEROL & Formoterol
- long-acting β_2-agonist (LABA) (selective)
- Single dose via dry powder inhaler = Bronchodilation over 12 hrs
- ∴ albuterol = 3 hr
- Salmeterol = somewhat delayed onset
- Formoterol = Rapid onset
- Effective / recomm. in comb ē corticosteroids
- DOC — Nocturnal Asthma*
- ↑se risk of Asthma-related deaths

OXYMETAZOLINE
α_1 = post sym smooth muscle
- D. Acting, Synthetic, α_1 & α_2
- In OTC short term nasal decongest; opthala. drop (for redness of eyes assoc. ē swimming, colds, contact lenses
- Cause vasoconstric → ↓ congestion
- Rebound congestion & dependence, Nervousness, Headache, Trouble sleeping
- local irritation & sneezing [intra-Nasal ADM]
- Abs. in systemic circu. regardless of route of adm.

α_{1a} = UT

α_{1b} = blood vessel.

CLONIDINE :- α_2-agonist
Act centrally (on pre-synp) control release of NE in symp-sys.
- Treat Hypertension (when 2 or more drug couldn't produce response)

Action of central pre-syp α_2-recep → inhibit Vasomotor centre → ↓ Symp. outflow to periphy → ↓ B.P

↓ symp. asso. ē opiates, Tobacco, & benzodiaze. withdrawal

ADR: lethargy, sedation, constip. & xerostomia (like antichol.)

Abrupt discontin = Rebound Hypertension

Doesn't affect RBF & GFR = so can be use in HT due to renal dise.

MIRABEGRON = β_3 agonist
- Relax detrusor muscle = ↑ bladder capacity [For overactive - Bladder]
- ↑ B.P
- ↑ Level of digoxin
- Inhibit CYP2D6 isozyme = ↑ metoprolol effect and other drugs effe

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]
- ↑ BP (α_1)
- Cardiac stimulation (β_1)
- ↑se NON-VESICULAR release of catecholamine (NOR epi & dopa) from nerve terminals.
- cross BBB

*Modafinil (brand)

→ For excretion = make urine acidic by NH_4Cl

→ Only Drug in doping Test of Athelet

TYRAMINE

- NOT useful clinically
- found in fermented food
  - aged cheese
  - chianti wine
- By-Product of Tyrosine metab.
- metab. by MAO
- If MAO inhibi given → vasopressor so epides occur
- Enter nerve terminal → displace stored NOR-epi

COCAINE

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

MIXED-ACTION AGONISTS (ephedrine & pseudoephedrine)

- release stored Norepi from nerve terminal
- Stimulate α & β recep.
- less potent
- are NOT CATECHOL → POOR substrate for COMT & MAO
- long duration
- excell absor.
- CNS penetra
- Incomp metab of pseudo
- unchange elim of ephe.

EPHEDRINE

- vasocons → ↑ sys. & dia. B.P (Treat Hypoten)
- Cardiac stimul.
- Bronchodil – BUT less potent & slower acting than epi & isopro.
- mild CNS-stimulant → Talkerness, ↓ 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.