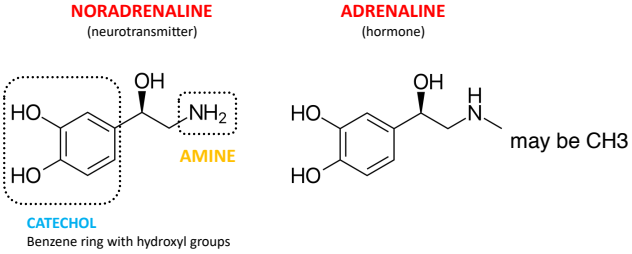
L6: ADRENERGIC

Tissue/Organ	Response	Receptor
heart	↑ HR, contraction force	β1
blood vessels	constriction	α1
blood vessels (skeletal muscle)	dilation: distribute blood to impt organs, fight/flight, movement	β2
bronchi	dilation	β2
GI tract	relaxation	β2
GI sphincters	contraction	α1
radial muscle (pupil)	contract outwards (pupil dilates)	α1
kidney	renin secretion: angiotensinogen → ANG I → ANG II	β1
liver skeletal muscle	liver glycogenolysis: glycogen breakdown → glucose to blood skeletal muscle → use up glycogen	β1

- adrenergic mediators (similar but not identical PHRM property): catecholamines (NA, A, DA)



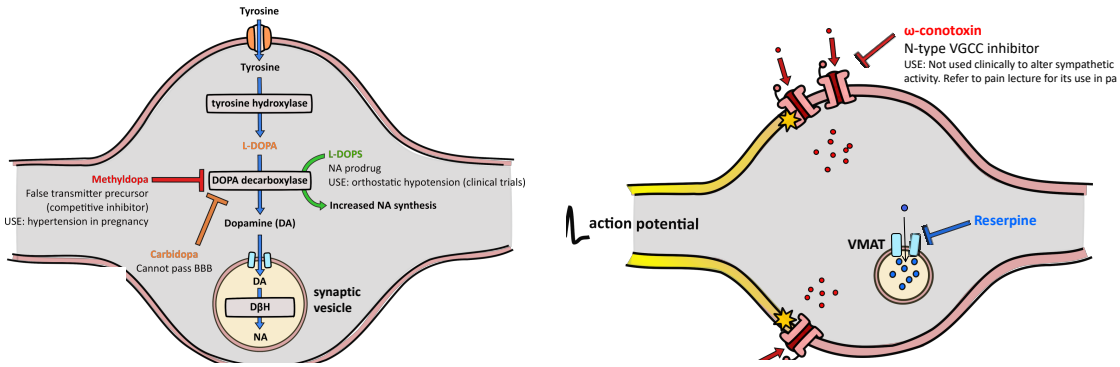
Catecholamine Synthesis

(1) sympathetic nerve terminals

- tyrosine → enter nerve terminals via transporter → tyrosine hydroxylase → L-DOPA (L-dihydroxyphenylalanine) → DOPA decarboxylase → dopamine → DA enter synaptic vesicle → DβH (dopamine β-hydroxylase) → NA
- Methyldopa: inhibit DOPA decarboxylase, competitive inhibitor, false transmitter precursor (✗ convert to DA)
  - hypertension in pregnancy: no side effect on fetus, risk vs reward
- L-DOPS: NA prodrug, not phrm active, need to be metabolised → active
  - orthostatic (postural) hypotension: stand up → blood goes to feet → BP ↓, faint
  - treat dysfunctional DβH → straight away L-DOPS to NA → ↑ HR, contractility, ↑ BP
- L-DOPA: ↑ DA synthesis → Parkinson (lost dopaminergic neurons)
- Carbidopa: block DOPA decarboxylase, adjunct therapy to L-DOPA (max effectiveness of primary therapy)
- L-DOPA & Carbidopa: counterintuitive

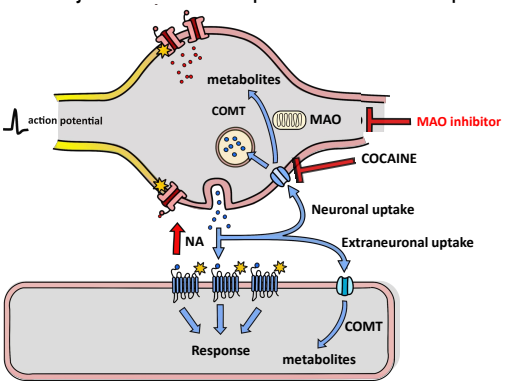
(2) adrenals

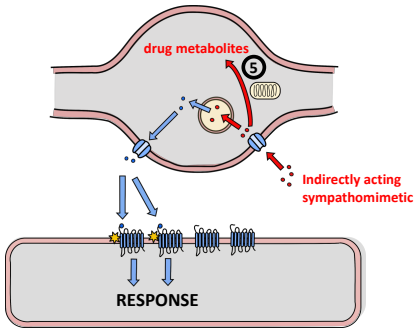
- DA into synaptic vesicle → DβH → NA → PNMT (phenylethanolamine-N-methyl transferase) → adrenaline



NT Release (Ca^{2+} dependent exocytosis)
- AP → depolarisation → open N-type voltage-gated Ca2+ channels → Ca2+ influx → ↑ i[Ca2+] → synaptic vesicle fuse to membrane → release NA
- ω-conotoxin: N-type VGCC inhibitor
  - used for pain / look at symp-mediated response, not to alter symp activity
- Reserpine: block VMAT (vesicular monoamine transporter) on vesicle membrane
  - hypertension: block A from entering vesicle → when vesicle fuse to membrane → release nothing

NT Inactivation
- neuronal uptake: NA ↑ affinity to transporter (NET, norepinephrine t.) → into nerve terminal → store in vesicle via VMAT
- extraneuronal uptake: ↓ affinity, uptake of NA to effector tissue via OCT3 transporter
- metabolism
  - MAO (monoamine oxidase) in mito → NA → metabolites [main way]
  - after extraneuronal uptake → COMT (catechol-O-methyltransferase) → metabolites
- Cocaine: inhibit neuronal uptake by NET → ↑NA in junction → prolonged response → stronger/longer contraction
- MAO inhibitor: antidepressant, inhibit NA from becoming metabolites → more NA in nerve terminal → into vesicles → more NA leak into junction → ↑ response of adrenoceptor





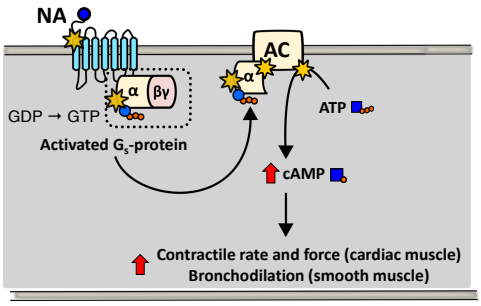
Indirectly Acting Sympathomimetics
- ✗ directly bind/stimulate adrenoceptors ; mimics endogenous agonist effect on symp
- sympathomimetic structurally similar to NA → transported by NET into terminal (limit NA neuronal uptake)
- VMAT store it in vesicles → NA displaced out from vesicles into terminal (cytosol)
- metabolised by MAO → inhibit metabolism/breakdown of NA → more drugs in terminals
- some NA escape via NET → ↑ NA in junction → ↑ NA response on adrenoceptors ⇨ sympathomimetic
- sympathomimetics + MAO-inhibitors → ↑ action
- Tyramine [dietary product — substrate for MAO], Amphetamine

Directly Acting Sympathomimetics (agonist)
- mimic response of activated symp
- catecholamines: NA (endogenous), A (endogenous), Isoprenaline/ISO (synthetic)
- non-catecholamines: Phenylephrine/PE (synthetic)

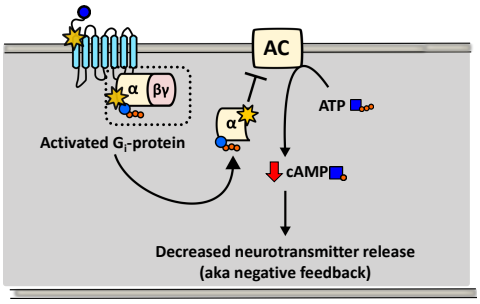
Potency of Sympathomimetics based on tissue response
- blood vessels (measure vasoconstriction): PE > NA ≥ A >> ISO
- heart (measure contractile force & rate): ISO > A ≥ NA >> PE
- tissues have diff adrenoceptors. sympathomimetics have diff selectivity for diff adrenoceptors

Adrenoceptors
- GPCR, coupled to & activate G-protein (numerous) → activate cellular enzyme → 2° messenger → intracell signalling cascade → cellular modulation
- ✓ selectivity
- signal transduction
  - **β1 & β2: Gs**
  - **α2: Gi**
    - orthoinhibitor receptor, at presynaptic nerve terminal, inhibit NA release
    - activate α2 → - FB → open K+ channels → hyperpolarisation → less activation of VGCC → ↓NA → ↓BP
  - **α1: Gq**
- benefit of selectively targeting receptor subtype (selective agonist)
  - elicit desired response, min adverse effects

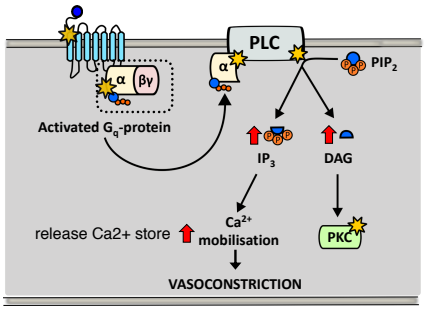
- pharmacogenetics
  - mol cloning confirm existence of adrenoceptor subtypes — genetic polymorphism
  - alter expression profile, receptor properties, func consequences (therapeutic drugs, personalised medicine)



β1 & β2



α2



α1

Receptor Subtype	α1	α2	α1 + α2	β1	β2	β1 + β2
G-protein	Gq	Gi		Gs	Gs	
2° messenger	↑ IP3 + DAG	↓ cAMP		↑ cAMP	↑ cAMP	
Response	vasoconstriction	↓ NT release		↑ cardiac muscle contractile rate/force	relaxation (smooth muscle)	
Localisation	vascular smooth muscle	symp presynaptic nerve terminal		heart, kidney	bronchi, blood vessels	
Agonists	Phenylephrine *nasal decongestant*	Clonidine *hypertension*		Dobutamine *heart failure → ↑ HR/ contractile force → ↑CO*	Salbutamol *asthma (bronchodilation)*	Isoprenaline
Antagonists	Prazosin *hypertension*	Yohimbine	Phentolamine	Atenolol *hypertension (less activation of heart)*		Propanolol