

PHARMACOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

- (a) *To describe the physiological roles of the sympathetic and parasympathetic nervous system.*
- (b) *To describe the physiological actions of adrenergic, cholinergic, and dopaminergic receptors including the subtypes and their cellular effects.*

Overview of the Autonomic Nervous System (ANS):

The hypothalamus regulates involuntary and unconscious visceral functions (involving smooth muscle, cardiac muscle, glands) responsible for maintaining homeostasis via a “neuroendocrine” outflow → ANS is a complex system of neurons involved in the “neural” aspect of this outflow

Note: ANS outflow is “involuntary/unconscious” and “continuous and tonic” (cf. somatic outflow, which is “voluntary/conscious” and “phasic”)

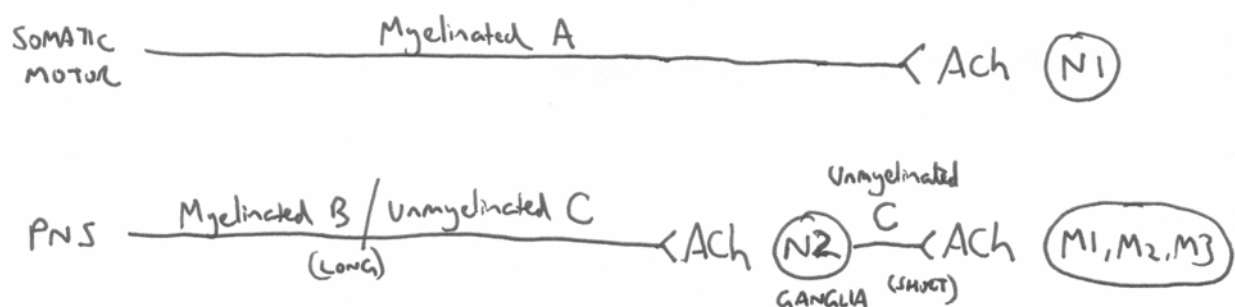
Anatomical components of the ANS:

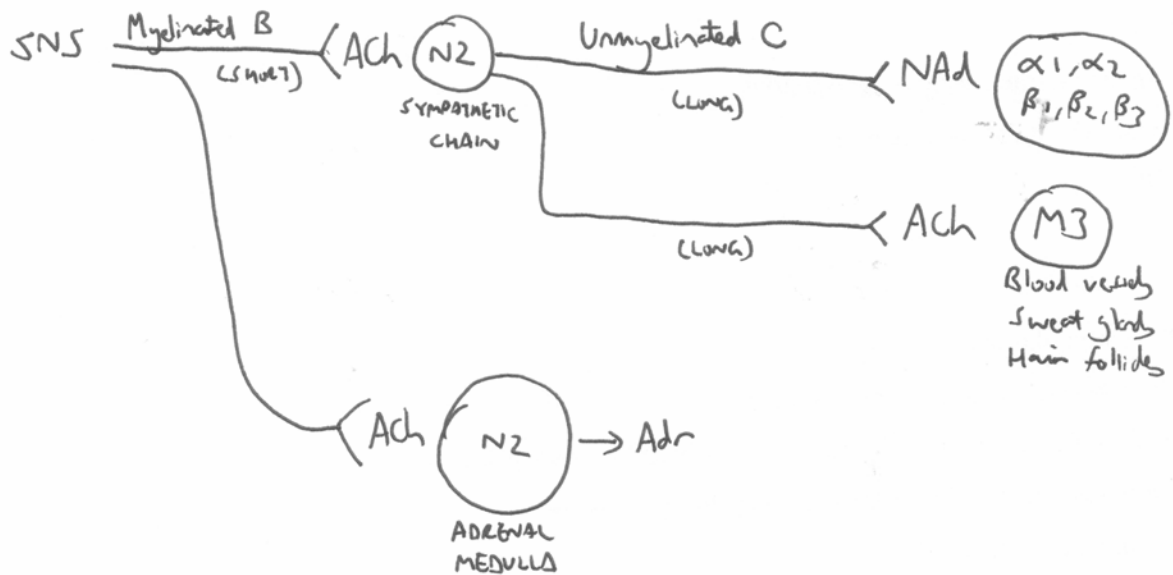
- (1) Afferent inputs → relay information regarding visceral sensations to CNS
 - Visceral receptors (Eg. chemo-, osmo- and mechanoreceptors) → unmyelinated afferent autonomic neurons → enter CNS by 2 paths:
 - (i) Via visceral nerves into the Sympathetic trunk → then reach DRG via the white or grey rami communicantes
 - (ii) Via somatic spinal nerves to reach DRG directly (without entering the Sympathetic chain)
 - “Multisynaptic” reflex arcs are formed – Autonomic afferent neurons synapse with interneurons of the dorsal horn → then synapse with preganglionic neurons of vagal nerve and/or thoracolumbar spine, and neurons of ascending spinal tracts to the brainstem
- (2) Central integration centre → integrates afferent visceral inputs to determine appropriate visceral response
 - Mainly hypothalamus (under influence by neocortex)
 - Also medulla (controls BRR), nerve plexuses in gut and spinal cord (controls ENS)
- (3) Efferent outputs → control function of individual viscera
 - Nerve fibres extend from the hypothalamus to specific brainstem and spinal cord regions (cranial, thoracolumbar and sacral regions) → then from these regions, efferent autonomic neurons are sent to effector organs
 - Involves two efferent autonomic nerves in SERIES – (i) Preganglionic nerve, and (ii) Postganglionic nerve – that connect at a ganglion
 - Ganglion can exist – (i) Alongside the vertebral column, (ii) In plexuses in the thorax or abdomen, or (iii) Within the target organ innervated

Functional divisions of the ANS:

- (1) Sympathetic nervous system (“Fight or flight”)
 - (a) Preganglionic nerves:
 - Originate from the lateral horn of the thoracic and upper lumbar spinal cord segments (T1 to L2) → leave the spinal cord through ventral roots with “spinal nerves” → then leave the spinal nerves as “white rami communicantes” (SHORT myelinated B fibres) to synapse with postganglionic nerves in the Sympathetic chain (ganglia) located close to the spinal cord

- These fibres release ACh onto nAChR (N2) on the postganglionic SNS nerves
 - (b) Sympathetic chain (ganglia) is divided into 3 parts:
 - (i) Cervical → supplies eyes, salivary glands and blood vessels of the head, neck, and thorax
 - (ii) Thoracic → supplies heart, lungs, thoracic and abdominal blood vessels, gut and kidneys
 - (iii) Lumbar → supplies descending colon, bladder and genitals
 - (c) Postganglionic nerves:
 - Leave the ganglia as “grey rami communicantes” (LONG unmyelinated C fibres) → join Spinal nerves or Visceral nerves to innervate the target organ
 - Generally release NAd onto Adrenergic receptors ($\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, $\beta 3$) on the target organ, EXCEPT on sweat glands, hair follicles and blood vessels of muscles (ACh on mAChR (M3))
 - (d) Adrenal gland:
 - Modified collection of sympathetic postganglionic neurons (chromaffin cells) that release Adr into the systemic circulation
 - Stimulated by ACh release from preganglionic neurons onto nAChR (N2)
- (2) Parasympathetic nervous system (“Rest and digest”)
- (a) Preganglionic nerves
 - Originate from brainstem (CN III, VII, IX, X) and sacral segments of spinal cord (S2-S4) → travel via LONG myelinated B or unmyelinated C fibres to synapse with ganglia close to or within their effector organs
 - These fibres release ACh onto nAChR (N2) on the postganglionic PNS nerves
 - (b) Postganglionic nerves:
 - Postganglionic PNS nerves are SHORT unmyelinated C fibres
 - All postganglionic PNS fibres release ACh onto mAChR (M1, M2, M3) on the target organ
 - (c) PNS outflow:
 - Cranial outflow → supply eye, salivary glands, heart, bronchi, upper GIT (to splenic flexure) and ureters
 - Sacral outflow → innervate descending colon/rectum, bladder, uterus and genitals
- (3) Enteric nervous system
- Consists of ganglionic plexuses within muscularis mucosa (submucosal plexus) and muscularis externa (myenteric plexu) → supplies SM, mucosa and blood vessels of GIT
 - These ganglia generally are not innervated by ANS neurons from CNS (I.e. possess intrinsic activity) → but they still receive minor inputs from (i) CN X or vagus (excitatory), and (ii) SNS outflow (inhibitory)





Adrenergic, cholinergic, and dopaminergic receptors:

Cholinergic receptors:

Receptor type	Receptor subtype	Location	MOA	Effect
Nicotinic (nAChR)	N1	Post-synaptic	Receptor-linked ion channel (2x α , β , γ , δ subunits) $\rightarrow$ ACh binds to each α -subunit opens channel $\rightarrow$ $\uparrow$ Na^+ influx $\gg$ K^+ efflux $\rightarrow$ depolarisation	NMJ (junctional and extrajunctional receptors) $\rightarrow$ skeletal muscle contraction
	N2	Pre- and post-synaptic		- ANS ganglia and adrenal medulla (post-synaptic) $\rightarrow$ efferent transmission of SNS and PNS and Adr release - NMJ (prejunctional or pre-synaptic) $\rightarrow$ +ve feedback on presynaptic ACh release - CNS
Muscarinic (mAChR)	M1	Post-synaptic	Gq	- CNS - Gastric parietal cell $\rightarrow$ gastric acid secretion
	M2	Post-synaptic	Gi	- Heart (SAN and AVN) $\rightarrow$ -ve chronotropy - Bronchial SM $\rightarrow$ bronchoconstriction - CNS
	M3	Post-synaptic	Gq	- CNS - Glandular tissue (lacrimal, salivary, GI, GU, respiratory and sweat glands) $\rightarrow$ $\uparrow$ secretions - Bronchial SM $\rightarrow$ bronchoconstriction - Vascular SM $\rightarrow$ vasodilation (via NO release) - GI and GU SM contraction of walls; relaxation of sphincters - Uterine contraction - Penile erection - Iris and ciliary muscle contraction
	M4	Post-synaptic	Gi	Unknown
	M5	Post-synaptic	Gq	Unknown

Adrenergic receptors:

Receptor type	Receptor subtype	Location	MOA	Effect
α	$\alpha 1$	Post-synaptic	Gq	- Peripheral vasoconstriction (skin, splanchnic, coronary) - Salivation - GI and GU SM relaxation - Mydriasis - Seminal vesicles/prostate and uterine SM contraction - Hepatic glycogenolysis
	$\alpha 2$	Pre-synaptic	Gi	Inhibits NAd release from ANS nerves $\rightarrow$ $\downarrow$ SNS response
		Post-synaptic	Gi	- Platelet aggregation - Hyperpolarisation of CNS neurons (sedation, analgesia) - $\downarrow$ insulin release from beta-pancreatic islet cells
β	$\beta 1$	Post-synaptic	Gs	- +ve inotropy and chronotropy ($\uparrow$ contractility/HR) - +ve dromotropy ($\uparrow$ electrical conduction $\rightarrow$ arrhythmias) - GI SM relaxation - Renin secretion from JG cells in JGA (kidney)
	$\beta 2$	Post-synaptic	Gs	- Bronchodilation and $\downarrow$ bronchial wall gland secretion - Vasodilation (esp skeletal muscle) - Uterine SM relaxation - GI SM relaxation - Muscle tremors - Hepatic glycogenolysis - Glucagon release from pancreas - Mast-cell inhibition of histamine release
	$\beta 3$	Post-synaptic	Gs	Lipolysis and thermogenesis at adipose tissue (esp brown fat) and skeletal muscle

Dopaminergic receptors:

Receptor type	Receptor subtype	Location	MOA	Effect
D1	D1 and D5	Post-synaptic	Gs	CNS – Nigrostriatal pathway (75%) $\rightarrow$ substantial nigra to corpus striatum $\rightarrow$ forms extrapyramidal system (motor function) Peripheral – Vasodilation of renal, mesenteric, coronary and cerebral blood vessels
D2	D2 – D4	Pre- and post-synaptic	Gi or Gq	CNS: - (a) Mesolimbic/mesocortical pathway $\rightarrow$ midbrain to limbic system (esp nucleus ambiguus and amygdaloid nucleus) and frontal cortex $\rightarrow$ role in emotion (reward) and behavioural effects (stereotyped behaviour patterns) - (b) Tuberohypophyseal pathway $\rightarrow$ ventral hypothalamus to median eminence and anterior pituitary gland $\rightarrow$ endocrine effects (inhibits PRL release and stimulates GH release) - (c) Medulla $\rightarrow$ forms chemoreceptor trigger zone (role in emesis) Peripheral – $\downarrow$ NAd release from post-ganglionic SNS nerve terminals

Remember:

- Gq $\rightarrow$ activate PLC $\rightarrow$ cleaves PIP2 into IP3 and DAG $\rightarrow$ $\uparrow$ IC $[Ca^{2+}]$ and activates PKC (respectively) $\rightarrow$ $\downarrow$ K^+ conductance and $\uparrow$ Ca^{2+} conductance $\rightarrow$ cell depolarisation
- Gi $\rightarrow$ inhibits AC $\rightarrow$ $\downarrow$ IC [cAMP] $\rightarrow$ $\downarrow$ PKA activation $\rightarrow$ $\uparrow$ opening of K^+ $\rightarrow$ cell hyperpolarisation
- Gs $\rightarrow$ activates AC $\rightarrow$ $\uparrow$ IC [cAMP] $\rightarrow$ $\uparrow$ PKA activation $\rightarrow$ cell depolarisation

Physiological roles of SNS and PNS:

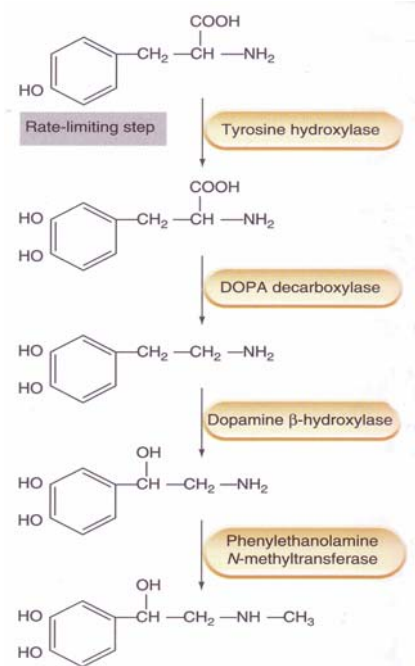
Target organ	SNS effect	
CVS	(i) +ve inotropic, chronotropic and dromotropic effects (β_1) (ii) Generally causes vasoconstriction (α_1) in skin, splanchnic viscera, kidneys and mucosa, but can cause vasodilation (β_2) in skeletal muscle (iii) AII release causing vasoconstriction (due to β_1 effects on renin secretion at JG cells)	(i) -ve chronotropic effect only (M2) (ii) No direct change in vasomotor tone (due to cholinergic innervation → but M3 causes NO release → cause vasodilation)
Lungs	(i) Bronchial SM relaxation (β_2) (ii) Pulmonary blood vessel vasoconstriction (iii) Reduced bronchial wall gland secretion (β_2)	(i) Bronchial SM contraction (M2/M3) (ii) Pulmonary blood vessel vasodilation (M3) (iii) Increased bronchial wall gland secretion (M3)
GI tract	(i) Increased sphincteric tone (pylorus, ileocolic and rectal sphincters) (ii) Inhibition of peristalsis and reduced GI motility (iii) Reduced GI secretions (iv) Constrict splanchnic arterioles to redistribute BV * All above via α and β effect *	(i) Relaxed sphincter tone (M3) (ii) Increased GI peristalsis and motility (M3) (iii) Increased GI secretions (M1/M3)
GU and reproductive tract	(i) Relaxes bladder detrusor muscle (ii) SM contraction of seminal vesicles and prostate (ejaculation) (α_1) (iii) Uterine contraction (α_1) and relaxation (β_2)	(i) Contracts bladder detrusor (M3) (ii) Erection (M3) (iii) Uterine contraction (M3)
Eyes	(i) Dilation of pupil (radial muscles) (α_1) (ii) Retraction of eyelid	Constriction of pupil (M3)
Cutaneous	(i) Piloerection (M3) (ii) Vasconstriction (α_1) (iii) Sweating (M3)	
Musculoskeletal	Arteriolar vasodilation and muscle tremor (β_2)	
Metabolic	(i) Hyperglycaemia – Hepatic glycogenolysis and glucagon release (β_2), Muscle glycogenolysis (β_1), and reduced insulin release (α) (ii) Lipolysis (β_1)	
Haematological	(i) Mast cell inhibition of histamine release (β_2) (ii) Platelet-aggregation (α_2)	

(c) *To describe the synthesis, fate and release of adrenergic and cholinergic transmitters.*

(I) Synthesis, fate and release of adrenergic transmitters:

Synthesis of adrenergic transmitters:

- (1) Tyrosine is derived from the diet OR hydroxylated from Phenylalanine in the liver (by Phenylalanine hydroxylase) → then actively concentrated in adrenergic nerve or adrenal medulla
- (2) Tyrosine is converted to DOPA by Tyrosine hydroxylase (*rate-determining step*) in the cytoplasm of adrenergic nerve or adrenal medulla
- (3) DOPA is then converted to DA via DOPA decarboxylase in the cytoplasm of adrenergic nerve or adrenal medulla
- (4) Vesicles (adrenergic nerve) or chromaffin granules (adrenal medulla) take up DA → converts it to NAd via DA β-hydroxylase
- (5) Within adrenal medulla only → 80% of chromaffin cells possess cytoplasmic Phenylethanolamine N-Methyl Transferase → NAd diffuses back into cytoplasm where it is N-methylated to Adr using S-adenosyl-methionine (SAM)



Storage and release of adrenergic transmitters:

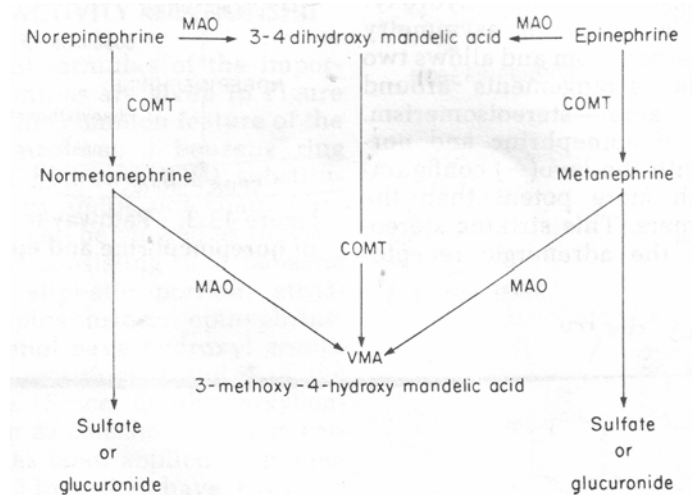
- Adrenergic transmitters are stored in – (i) “vesicles” in nerve terminal of adrenergic neuron (NAd only), or (ii) “chromaffin granule” in chromaffin cells of the adrenal medulla (80% cells → Adr; 20% cells → NAd)
- These storage vesicles and granules contains – (i) Adr or NAd, (ii) ATP, (iii) chromogranin
- These transmitters are released in response to depolarisation of the nerve terminal (by nerve AP) or chromaffin cells (by N2 nAChR activation by ACh from preganglionic SNS fibres) → induces Ca^{2+} influx → Ca^{2+} -dependent exocytosis of adrenergic transmitter stores
- Adr and NAd then act on pre-synaptic adrenoceptors (α_2 → -ve feedback) and post-synaptic adrenoceptors ($\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$ → produce effect in target cell)

Note: Adrenergic transmitters have very short $t_{1/2}$ (Adr 10-15 sec; NAd 20-30 sec) → due to rapid uptake and metabolism (see below)

Inactivation of adrenergic transmitters:

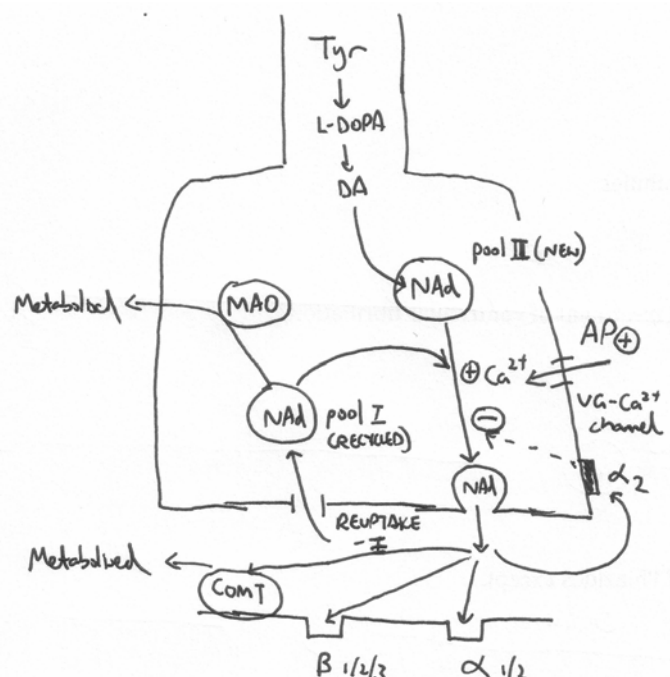
- (1) Non-enzymatic mechanisms:
 - (a) Post-ganglionic SNS nerve terminal reuptake (uptake 1) → actively takes up synaptic or circulating adrenergic transmitters for intraneuronal storage/recycling and enzymatic metabolism
 - (b) Extraneuronal (tissue) uptake in lungs, liver, kidney and gut (uptake 2) → actively takes up circulating adrenergic transmitters for enzymatic metabolism
- (2) Enzymatic mechanisms:
 - (a) Monoamine Oxidase (MAO)
 - Non-specific deaminase found in → (i) mitochondria of extraneuronal tissues (lungs, liver, kidney and gut) and (ii) cytoplasm of post-ganglionic SNS nerve terminals
 - Performs oxidative deamination of adrenergic transmitters taken up by these tissues:
 - (i) NAd/Adr → to 3,4-dihydroxy-mandelic acid

- (ii) Methylated metabolites of NAd/Adr (normetanephrine, metanephrine) → to 3-methoxy-4-hydroxy-mandelic acid (aka. VMA)
- (b) Catechol-O-methyl transferase (COMT)
- Methyl transferase found in → (i) extraneuronal tissues (only liver and kidney), and (ii) post-synaptic membrane of target tissues
 - Performs methylation (using SAM) of OH group of adrenergic transmitter:
 - (i) NAd/Adr → to normetanephrine/metanephrine
 - (ii) 3,4-dihydroxy-mandelic acid → to 3-methoxy-4-hydroxy-mandelic acid
- (c) Conjugation reactions → Normetanephrine and metanephrine are conjugated with sulphate/glucuronide



- Adrenergic transmitter metabolites are then renally excreted:
- 97% excreted as deaminated and methylated metabolites (VMA and MOPG (3-methoxy-4-hydroxy-phenyl glycol))
 - 3% excreted as methylated metabolites (normetanephrine/metanephrine) conjugated with sulphate/glucuronide

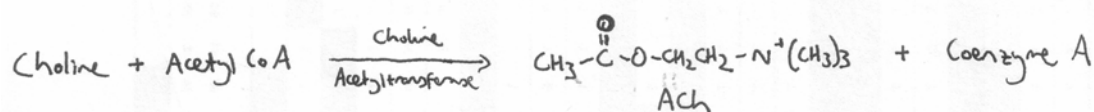
Note: Urinary VMA/MOPG reflect general SNS activity (as majority of metabolites derived from NAd rather than Adr); while plasma or urinary Adr better reflects adrenal medullary function



(II) Synthesis, fate and release of cholinergic transmitters:

Synthesis of cholinergic transmitters:

- ACh is synthesised in the axoplasm of the cholinergic nerve terminal – It is formed by the acetylation of Choline (derived from diet or recycled from ACh metabolism) with Acetyl-CoA (derived from pyruvate) using the enzyme Choline acetyltransferase



Synthesis and release of cholinergic transmitters:

- ACh is stored in synaptic vesicles in the nerve terminal → released into synaptic cleft when a nerve AP depolarises the nerve terminal → opens Ca^{2+} channels and ↑ influx of Ca^{2+} → induces Ca^{2+} -dependent exocytosis of vesicular-ACh stores

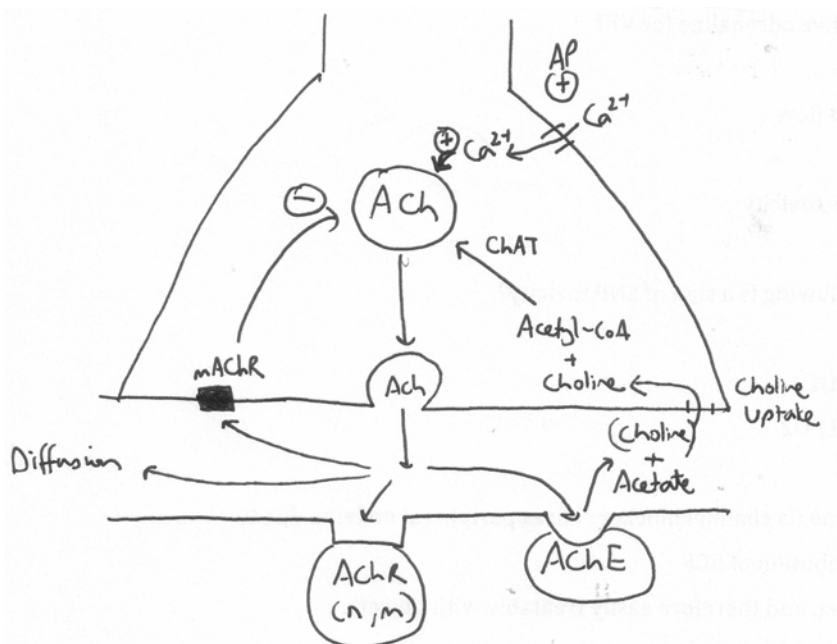
Note:

- 1 quanta of ACh = 100-200 synaptic vesicles = 5000-10,000 ACh molecules
- Single nerve impulse → release > 200 quanta of ACh

- ACh diffuses across the synaptic cleft and binds to presynaptic mAChR (-ve feedback) and/or postsynaptic mAChR or nAChR (produce effect in target cell)

Inactivation of adrenergic transmitters:

- (1) Acetylcholinesterase (aka. True cholinesterase)
 - o Found at all synapses involving cholinergic transmission (nicotinic and muscarinic)
 - o Main role – Control duration of ACh receptor activation → terminates the effect of synaptic ACh by rapidly and efficiently hydrolysing it (Nb. 300k ACh metabolised per minute such that only 50% of released ACh reaches the target receptor!), thus preventing prolonged receptor activation/target membrane depolarisation
 - o Contains (i) anionic binding site – Binds +vely charged quaternary ammonium on ACh, and (ii) esteratic binding site – Hydrolyses ester link in ACh to release choline (which is taken up into nerve terminal) and causes AChE to be acetylated. Acetylated AChE is rapidly hydrolysed to release acetic acid and regenerate the enzyme
- (2) ACh diffuses away from synapse
- (3) Choline uptake via a high affinity Na^+ -dependent system → recycled



- (d) **To describe the structure activity relationships of adrenergic and cholinergic agents.**
(Nb. See "Anticholinergic drugs" for structure-activity relationships of cholinergic agents)
- (e) **To compare and contrast the mechanism of action and effects of sympathomimetic and cholinomimetic agents used clinically.** (Nb. Cholinomimetic agents are not commonly used in anaesthesia nor in the primary exams – they will not be covered)
- (f) **To describe pharmacology of the alpha 1, alpha 2, beta 1 and beta 2 adrenergic agonists and their clinical applications.**
- (g) **To describe clinically important drug interactions with the autonomic nervous system.**

(I) Overview of Sympathomimetic Agents:

Definition of a sympathomimetic agent:

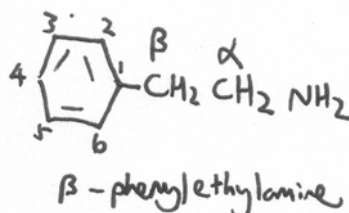
- A drug that evokes physiological responses mimicking endogenous SNS activity via action on adrenoceptors or dopamine receptors either – (i) directly (I.e. bind to and act directly via these receptors), or (ii) indirectly (I.e. cause release of NAd from post-ganglionic SNS nerve terminals to produce effects via these receptors)

Types of sympathomimetic agents:

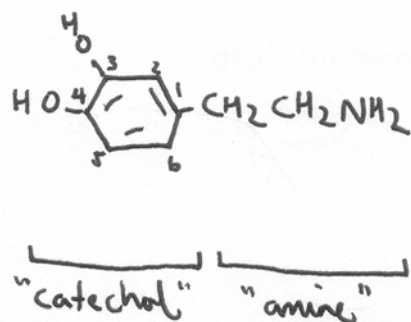
- (1) Naturally-occurring catecholamines (all direct acting) → Adr, NAd, DA
- (2) Synthetic catecholamines (all direct acting) → Isoprenaline, dobutamine, dopexamine
- (3) Synthetic noncatecholamines (direct and indirect acting) → Ephedrine, metaraminol, amphetamine, phenylephrine, methoxamine

Structure-activity relationship of sympathomimetic agents:

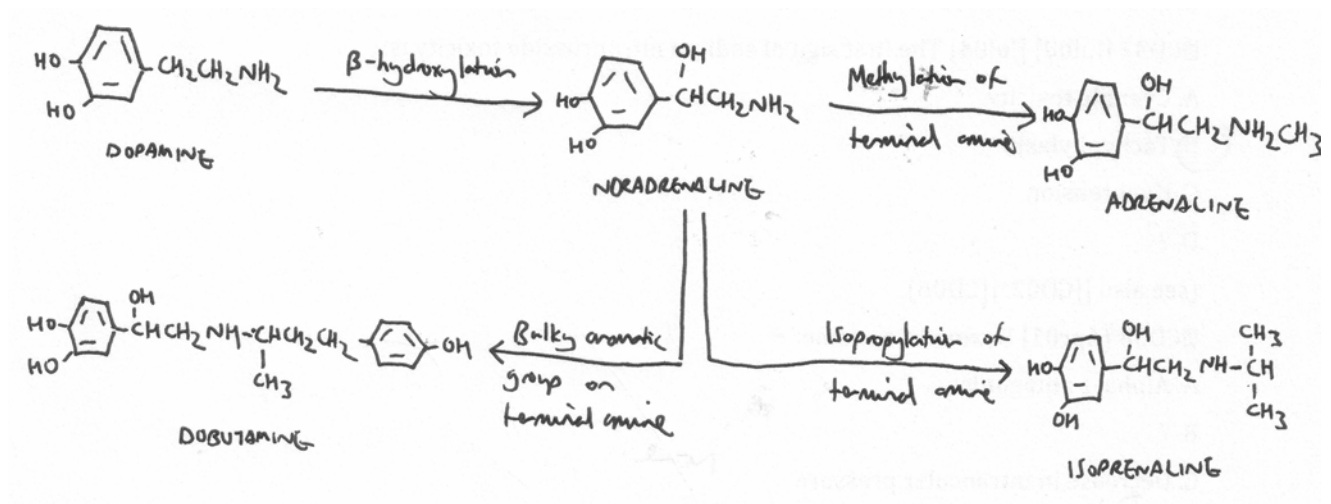
- All sympathomimetics agents are derived from → β -phenylethylamine



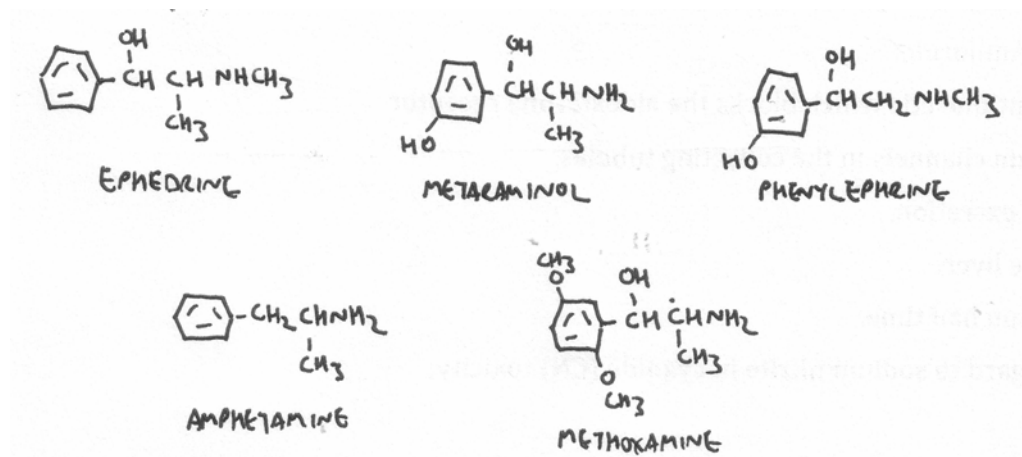
- Basic structure of catecholamines → consists of OH groups present at C3 and C4 positions on benzene ring (3,4-dihydroxybenzene → "catechol group") of a β -phenylethylamine structure



- ① Catechol - OH @ C3/C4 on benzene
- ② Amine - various amine side-chain @ C1 on benzene



- Basic structure of non-catecholamines $\rightarrow$ consists of β -phenylethylamine structure without OH groups on C3 and C4 positions on benzene ring (I.e. lack "catechol" group)



Structure-activity relationship:

- (1) Isomeric effect on activity $\rightarrow$ L-isomer is MORE active than D-isomer
- (2) Receptor selectivity:
 - o (i) Agonist activity at α and β receptor activity
 - Maximal effect if OH on C3 and C4 positions on benzene ring (I.e. all catecholamines) – Nb. $\downarrow$ effect if lacking either OH on C3 or C4 positions, or both (I.e. non-catecholamines)
 - $\uparrow$ activity with presence of β -OH of ethylamine (Eg. Adr, NAd, ephedrine, metaraminol)
 - o (ii) α receptor selectivity $\rightarrow$ Presence of α -methyl group (Eg. metaraminol)
 - o (iii) α_1 receptor selectivity $\rightarrow$ Lack OH on C4 position of benzene ring (Eg. phenylephrine)
 - o (iv) β receptor selectivity $\rightarrow$ Alkyl substitution of terminal amine of β -phenylethylamine (Eg. isoprenaline, adrenaline, dobutamine)
 - o (v) β_2 receptor selectivity $\rightarrow$ OH on C3 and C5 positions of benzene ring and alkyl group substitution on terminal amine (Eg. salbutamol) – Nb. Duration of action $\uparrow$ with bulkier substitutions due to $\uparrow$ lipophilicity and binding to β -receptor (Eg. salmeterol)
- (3) CNS stimulant effect:
 - o (i) Substituents on benzene ring:
 - No substituents (Eg. amphetamine) $\rightarrow \uparrow$ lipid solubility and $\uparrow$ CNS stimulation
 - Substituents present (Eg. all catecholamines) $\rightarrow \downarrow$ lipid solubility and $\downarrow$ CNS stimulation
 - o (ii) Presence of β -OH of ethylamine OH group (Eg. Adr, NAd, ephedrine, metaraminol) $\rightarrow \downarrow$ lipid solubility and $\downarrow$ CNS stimulation
- (4) Metabolism:
 - o COMT metabolism $\rightarrow$ Requires OH on C3 on benzene
 - o MAO metabolism $\rightarrow \downarrow$ with α -methyl group and/or bulky alkyl group on terminal amine

Mechanism of action of sympathomimetic agents:

- Evoke physiological responses mimicking endogenous SNS activity of the SNS by activating α -adrenoceptors, β -adrenoceptors or dopaminergic receptors
- Mechanism by which these receptors are activated depends on the type of agent:
 - (i) Indirect-acting agents (most synthetic non-catecholamines)
 - Evoke release of endogenous NAd from postganglionic SNS nerve ending by entering the nerve ending and displacing NAd into synaptic cleft → causes NAd to bind adrenoceptors
 - Produce mainly α and β_1 agonist effects (as NAd is a weak β_2 agonist)
 - Note – Denervation/depletion of NAd (I.e. repeated dosing) → blunts response of agent
 - (ii) Direct-acting agents (all catecholamines (natural and synthetic) and few synthetic non-catecholamines (Eg. phenylephrine, methoxamine))
 - Bind to adrenoceptor or dopamine receptor and activate them directly
 - Produce both α and β agonist effects (but magnitude of α and β activity varies as per agent)
 - Note – Denervation/depletion of NAd (I.e. repeated dosing) → does not alter response of drug

Pharmacokinetics of sympathomimetic agents:

- Absorption:
 - Catecholamines (synthetic and natural) → cannot be given orally (as they are metabolised by GIT mucosa and liver), and must be given parentally (esp IV)
 - Synthetic non-catecholamines → absence of one or both OH groups on C3/C4 positions of benzene ring or presence of α -methyl group on ethylamine allows ↑ oral absorption of drug
- Distribution:
 - Catecholamines (synthetic and natural) → cannot cross BBB or placenta due to ↓ lipid solubility (due to presence of β -OH on ethylamine and substituents on benzene ring)
 - Synthetic catecholamines → ↑ ability to cross BBB or placenta due to ↑ lipid solubility (due to ↓ substituents on benzene ring and/or lack of β -OH on ethylamine, esp with amphetamine)
- Metabolism/Excretion:
 - Catecholamines → Agents with “catechol” group are rapidly cleared by (i) enzymatic metabolism (COMT, MAO, conjugation) and (ii) non-enzymatic metabolism (uptake into extraneuronal tissue (lungs, liver, kidney, GIT) and post-ganglionic SNS nerve terminal) – See “inactivation of adrenergic transmitters” above
 - Synthetic noncatecholamines:
 - Lack of OH on C3 on benzene (Eg. ephedrine, amphetamine) → not metabolised by COMT, and thus ↑ dependence on MAO metabolism (Nb. use of MAOi vastly ↑↑↑ their duration of action and effect!)
 - Presence of α -methyl group (most agents) → ↑ resistance to metabolism by MAO
 - ↑ urinary excretion of unchanged drug if urine is acidified (as drug $pK_a > 9$)

(II) Naturally-Occurring Catecholamines:

(1) Adrenaline:

- Presentation and dosing:
 - Clear colourless solution as adrenaline HCl for IV (0.1-1 mg/mL)
 - Diluted in D5W (acidic environment) → prevents oxidation caused by alkalinity

- Given as either an IV bolus (0.1-1 mg) or IV infusion (0.01-1 ug/kg/min) → rapid onset with short-lasting effects (1-5 mins)
 - 1% ophthalmic solution
- Clinical uses:
 - (i) Treat asystolic cardiac arrest (10 ug/kg IV bolus)
 - (ii) Treat anaphylaxis/anaphylactoid reactions (1-10 ug/kg IV bolus, titrated to effect)
 - (iii) Vaso- and inotropic support in critically ill with low C.O. states (0.01-1 ug/kg/min IV infusion, titrated to effect)
 - (iv) Reduce swelling associated with UAW obstruction (nebulised)
 - (v) Treat refractory bronchoconstriction (nebulised)
 - (vi) Treat open-angle glaucoma (1% ophthalmic solution)
 - (vii) Combined with LA solution (1:80-200k) to cause localised VC → ↓ systemic absorption and ↑ duration of action of LA
- Mechanism of action – Direct-acting sympathomimetic agent with equal agonist effects on α and β receptors
- Pharmacokinetics:

Absorption	- Cannot be given PO (due to metabolism in GIT mucosa and liver) - Given parentally only – IV > IM > S/C (due to localised vasoconstriction). Can also be given nebulised or via ETT (erratic absorption).
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)
Metabolism/ Elimination	- Clearance via enzymatic metabolism and non-enzymatic route (see above) - Elimination $t_{1/2}$ 2 mins (due to rapid clearance/metabolism)

- Pharmacodynamic effects:

CVS	- Low dose IVI (< 5 ug/min) → β effects ○ ↑ C.O. due to ↑ HR and contractility (+ve chrono- and inotropy) and ↑ venous return (β_1) ○ ↓SVR due to skeletal muscle vasodilation (β_2) ○ BP effects – ↑ SBP (due to ↑ C.O.) and ↓ DBP (due to ↓ SVR) → MAP unchanged and ↑ pulse pressure ○ ↑ coronary blood flow due to coronary vasodilation (β_1) ○ ↑ cardiac MRO_2 due to ↑ HR/contractility (β_1) ○ Absence of BRR-mediated reflex bradycardia due to no change in MAP - High dose IVI (10-20 ug/min) or IV bolus (10 ug/kg) → both α and β effects ○ ↑ SVR due to vasoconstriction in skin, mucosa, splanchnic and renal vasculature (α_1) → redistributes C.O. (and blood flow) to skeletal muscles ○ Also above β effects
Respiratory	- Potent bronchodilator (β_2) - ↑ viscosity of secretions (β_2) - Respiratory stimulant (↑ MV due to ↑ TV and RR) - ↑ PAP due to ↑ PVR (α_1)
CNS/ocular	- Limited CNS effects due to ↓ lipid solubility → ↑ MAC and anaesthetic requirements), ↑ pain threshold - Mydriasis due to contraction of radial muscle of iris (α)
GI and GU effects	- ↓ RBF and splanchnic blood flow (α) - ↑ renal Na^+/H₂O reabsorption – Direct tubular effect on Na^+ transport, and indirect effect via RAAS activation (β_1) - Difficulty with micturition – ↑ sphincter tone (α); ↓ bladder tone (β) - Relaxes pregnant uterus (β_2) - Relaxes GI SM (α and β)
Metabolic	- ↑ BMR (20-30%)

	- ↑ BGL – ↑ hepatic/skeletal muscle glycogenolysis (β_1, β_2), ↑ hepatic gluconeogenesis (β_2), ↑ glucagon (β_2), variable effect on insulin (↑ secretion initially (β_2), then ↓ secretion (α_2)) - ↑ FFA (due to ↑ lipolysis 2° to ↑ lipase activity) → results in ↑ hepatic FA [O] and ketogenesis (β_1) - ↑ serum lactate due to ↑ skeletal muscle glycogenolysis - ↑ renin release (β_1) → ↑ AII and aldosterone effects - Serum K^+ – Initially ↑ [K^+] due to release from liver, but later ↓ [K^+] due to uptake into skeletal muscle (activates Na^+/K^+-ATPase) (β_2) - Mast cell stabilisation (β_2)
Issues and side-effects	- Extravasation → local vasoconstriction causing tissue necrosis (hence, requires CVC) - Should not be infiltrated into end-artery organ → compromises vascular supply - Unwanted CVS effects: - o ↑ arrhythmias due to ↑ rate of spontaneous phase 4 depolarisation) → esp arrhythmogenic with halothane - o Myocardial ischaemia due to ↑ cardiac MRO_2 - o Unwanted HTN and tachycardia - Hypercoagulable state (↑ CF V activity and platelet adhesiveness) - Risk of ↑ BGL and ketogenesis if used in DM patients - Difficulty with micturition (see above) - Unwanted excitatory CNS effects (anxiety, restlessness, headaches)

Aside: Overdose of sympathomimetics with α agonist effects (Adr and phenylephrine)

- Generally occurs with inadvertent systemic absorption from topical, S/C or regional anaesthesia use (I.e. Adr with LA) → causes HTN, tachycardia, BRR-mediated ↓ C.O.,
- Management involves either:
 - o No treatment at all → Adr and phenylephrine effects are brief and these CVS effects resolve spontaneously!
 - o If CVS effects are severe (I.e. hypertensive crisis) → consider vasodilating drugs (SNP, GTN) that do NOT ↓ HR or myocardial contractility

Note – Do NOT give β -blockers as they can precipitate APO and CVS collapse → this is b/c excess α stimulation causes ↑ SVR → causes heart to face ↑ afterload and ↑ preload (as blood is shifted from systemic → pulmonary circulation)) → β -blockers suppress compensatory +ve ino- and chronotropic mechanisms that preserve C.O. during this situation

(2) Noradrenaline:

- Presentation and dosing:
 - o Clear colourless solution as noradrenaline bitartrate for IV (0.2-2 mg/mL) → contains Na metabisulphite
 - o Diluted in D5W (acidic environment) → prevents oxidation caused by alkalinity
 - o Given as an IV infusion (0.05-0.5 ug/kg/min) → rapid onset with short-lasting effects (1-5 mins)
- Clinical uses – Vaso- and inotropic support in critically ill with shock and refractory hypotension
- Mechanism of action – Direct-acting sympathomimetic agent with predominantly α effects (esp at α_1), but also some β effects (as effect as Adr on β_1 ; minimal effect on β_2)
- Pharmacokinetics:

Absorption	- Cannot be given PO (due to metabolism in GIT mucosa and liver) - Given via IV route only
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)

Metabolism/ Elimination	- Clearance via enzymatic metabolism and non-enzymatic route (see above) - Elimination $t_{1/2}$ 2 mins (due to rapid clearance/metabolism)
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- Pharmacodynamic effects:

CVS	- $\uparrow$ SVR due to α_1-mediated vasoconstriction within skin, skeletal muscle, renal and splanchnic vasculature $\rightarrow$ causes $\uparrow$ BP (SBP, DBP and MAP) - $\downarrow$ C.O. due to (i) BRR-mediated $\downarrow$ HR and contractility a/w $\uparrow$ MAP and (ii) $\downarrow$ venous return a/w peripheral vasoconstriction - $\uparrow$ cardiac MRO_2 - $\uparrow$ coronary blood flow (due to coronary vasodilation)
Respiratory	- $\uparrow$ PAP due to $\uparrow$ PVR (α_1) - Very mild respiratory stimulant ($\uparrow$ MV due to $\uparrow$ TV and RR) and bronchodilator effect
CNS/ocular	- $\downarrow$ cerebral blood flow (α_1) - Mydriasis due to contraction of radial muscle of iris (α)
GI and GU effects	- $\downarrow$ RBF and splanchnic blood flow (α_1) - $\downarrow$ uterine blood flow and contracts pregnant uterus (α_1)
Metabolic	- $\uparrow$ BGL due to $\downarrow$ insulin secretion (α) - $\uparrow$ FFA (due to $\uparrow$ lipolysis 2° to $\uparrow$ lipase activity) $\rightarrow$ results in $\uparrow$ hepatic FA [O] and ketogenesis (β_1) - $\uparrow$ renin release (β_1) $\rightarrow$ $\uparrow$ AII and aldosterone effects
Issues and side-effects	- Extravasation $\rightarrow$ local vasoconstriction causing tissue necrosis (hence, requires CVC) - Obstetrics issue – Risk of foetal bradycardia and asphyxia (due to $\downarrow$ uterine blood flow and uterine contraction) - Caution in pts on MAOi $\rightarrow$ effects can be prolonged and/or exaggerated (I.e. HTN crisis) despite drug being direct-acting! - Unwanted CVS effects: - o $\uparrow$ arrhythmias $\rightarrow$ esp arrhythmogenic with halothane - o Myocardial ischaemia due to $\uparrow$ cardiac MRO_2 - o Unwanted HTN and bradycardia - o Excessive peripheral vasoconstriction $\rightarrow$ ischaemia and gangrene of extreme - Metabolic acidosis (due to $\downarrow$ tissue blood flow with vasoconstriction) - Risk of $\uparrow$ BGL and ketogenesis if used in DM patients - Unwanted CNS effects (anxiety, restlessness, headaches)

(3) Dopamine:

- Presentation and dosing:

- o Clear colourless solution of dopamine HCl for IV (40 or 160 mg/mL) $\rightarrow$ contains Na metabisulphite
- o Diluted in D5W (acidic environment) $\rightarrow$ prevents oxidation caused by alkalinity
- o Given as IV infusion (1-20 ug/kg/min, titrated to response) $\rightarrow$ onset within 5 mins, lasting 10 minutes

- Clinical uses:

- o (i) Treat shock a/w low C.O. states
- o (ii) Treat hypotension a/w septic shock
- o (iii) Prevent impending hepatic and renal failure

Note – DA is the only catecholamine that simultaneously $\uparrow$ myocardial contractility, $\uparrow$ RBF/GFR, and $\uparrow$ urine output (diuresis and natriuresis)

Aside: Renal dose of DA

- Low dose IVI (1-3 ug/kg/min) was given to pts at risk of ARF (I.e. AAA cross-clamping, cardiopulmonary bypass)
- BUT there is no evidence of renal protection → causes ↑ diuresis w/o affecting creatinine clearance or renal function if given prior to renal insult; no renal protection if given after renal insult established
- ALSO it causes potential harm (tachycardia/arrhythmias, myocardial ischaemia, ↓ ventilatory response to hypoxaemia, intrapulmonary shunting, mesenteric ischaemia causing bacterial translocation)

- Mechanism of action – Direct-acting effect with agonist activity at D1, D2, α and β receptors, and indirect-acting effects (stimulates release of endogenous NAD)

- Pharmacokinetics:

Absorption	- Cannot be given PO (due to metabolism in GIT mucosa and liver) - Given via IV route only
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)
Metabolism/ Elimination	- Clearance via enzymatic metabolism and non-enzymatic route (see above) - 25% of IV dose is converted to NAD in post-ganglionic SNS nerve terminals - Elimination $t_{1/2}$ 3 mins (due to rapid clearance/metabolism)

- Pharmacodynamic effects:

Low dose (1-5 ug/kg/min IV) → D1 in renal vasculature

Intermediate dose (5-10 ug/kg/min IV) → β 1 in heart

High dose (> 15 ug/kg/min IV) → α receptors in vasculature

CVS	- Low dose (< 10 ug/kg/min) → direct β1 effects (and also indirect sympathomimetic effects) ○ ↑ HR and contractility (+ve chrono- and inotropy) → ↑ C.O. and BP ○ ↑ coronary blood flow - High dose (> 15 ug/kg/min) → α effects ○ ↑ SVR and venous return
Respiratory	- ↑ PAP due to ↑ PVR (α1) - Attenuates ventilatory response to hypoxaemia (via effect at carotid bodies)
CNS/ocular	- Limited CNS effects – Modulates extrapyramidal movements (D1) and ↓ PRL secretion from pituitary gland (D2) - Stimulates CTZ → causes N/V (D2) - ↑ IOP
GI and GU effects	- ↑ renal and splanchnic blood flow due to vasodilation (low dose 1-5 ug/kg/min → direct D1 effect) and ↑ C.O. - ↑ urine output due to ↑ RBF (a/w renal vasodilation and ↑ C.O.) and inhibition of proximal tubular Na^+ reabsorption - ↑ gastric transit time
Metabolic	- ↑ BGL due to ↓ insulin secretion (α)
Issues and side-effects	- Extravasation → local vasoconstriction causing tissue necrosis (hence, requires CVC) - Caution in pts on MAOi → effects can be prolonged and/or exaggerated (I.e. HTN crisis) despite drug being direct-acting! - Unwanted CVS effects: ○ ↑ arrhythmias → esp arrhythmogenic with halothane (BUT less than adrenaline) ○ Myocardial ischaemia due to ↑ cardiac MRO_2 ○ Unwanted HTN and tachycardia - ↓ ventilatory response to hypoxaemia and intrapulmonary shunting - Nausea and vomiting

	- Issues with glaucoma (due to ↑ IOP)
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(III) Synthetic Catecholamines:

(1) Isoprenaline:

- Presentation and dosing:
 - o Clear colourless solution of isoprenaline HCl for IV (1 mg/mL)
 - o Given as IV infusion (0.5-10 ug/min)
- Clinical uses:
 - o (i) Treat severe bradycardia a/w β blockers or AV block (esp CHB whilst awaiting transvenous pacing/PPM insertion)
 - o (ii) Formerly used as a bronchodilator (but ↑ mortality risk; also replaced by β_2 agonists) and an inotropic agent (replaced by PDEi and dobutamine)
- Mechanism of action – Potent direct-acting sympathomimetic with agonist activity at β_1 and β_2 receptors (no α effects!)
- Pharmacokinetics:

Absorption	- Can be given PO (well-absorbed but extensive hepatic first-pass metabolism) - Usually given via IV route
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)
Metabolism/ Elimination	- Rapid clearance due to (i) metabolism by hepatic COMT, and (ii) excretion in urine unchanged (up to 75% of dose) - 25% of IV dose is converted to NAd in post-ganglionic SNS nerve terminals - Elimination $t_{1/2}$ 1-7 mins (due to rapid clearance/metabolism)

- Pharmacodynamic effects:

CVS	- ↑ C.O. 2° to ↑ HR/contractility (+ve chrono- and inotropy) (β_1) - ↑ automaticity and AVN conduction (β_1) - ↓ SVR due to vasodilation in skeletal muscle (β_2) - Effect on BP – ↑ SBP (due to ↑ C.O.), ↓ DBP (due to ↓ SVR), ↓ MAP due to ↓ DBP - ↑ cardiac MRO ₂ due to ↑ HR/contractility - ↓ coronary blood flow due to ↓ diastolic perfusion time (a/w tachycardia) and ↓ DBP (↓ coronary perfusion); mild offset by β_2 -mediated coronary vasodilation
Respiratory	- Potent bronchodilator (β_2) → ↑ anatomic dead space (V/Q mismatching) - Inhibits histamine release in lungs → improves mucous flow (β_2)
CNS	- CNS stimulant effect
GI and GU effects	- ↑ RBF and splanchnic blood flow - ↓ uterine tone
Metabolic	- ↑ BGL and FFA (β_1/β_2) - ↑ renin release (β_1) → ↑ AII and aldosterone effects
Issues and side-effects	- Tachyphylaxis with prolonged use - Unwanted CVS effects: - o ↑ arrhythmias → esp arrhythmogenic with halothane, hypoxaemia and hypercapnoea - o Myocardial ischaemia (not ideal for pts with IHD) due to ↑ cardiac MRO₂ and ↓ coronary blood flow - o Hypotension and excessive tachycardia

(2) Dobutamine:

- Overview – A derivative of isoprenaline with 2 isomers
- Presentation and dosing:

- Clear colourless solution of dobutamine HCl for IV (12.5 or 50 mg/mL; former with Na metabisulphite, latter with ascorbic acid)
- Diluted in D5W (acidic environment) → prevents oxidation caused by alkalinity
- Given as IV infusion (0.5-40 ug/kg/min, titrated to response) → onset in 1-2 mins
- Clinical uses:
 - (i) Augment low C.O. states a/w MI, cardiomyopathy, cardiac surgery and cardiogenic/septic shock
 - (ii) Used for cardiac stress testing (alt to exercise)
- Mechanism of action:
 - Direct-acting sympathomimetic with agonist activity mainly at β_1 receptor (minor effect at β_2 receptor)
 - Both isomers have β_1 -agonist effects, while L-isomer has α_1 agonist effects and R-isomer has α_1 antagonist effects
- Pharmacokinetics:

Absorption	Given via IV route only
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)
Metabolism/ Elimination	- Rapid metabolism by hepatic COMT into inactive metabolites → conjugated and excreted in urine - Elimination $t_{1/2}$ 2 mins (due to rapid metabolism)

- Pharmacodynamic effects:

Low doses (< 5 ug/kg/min) → potent β_1 -agonist effects

Higher doses (> 5 ug/kg/min) → α_1 -agonist effect of L-isomer apparent

CVS	- ↑ HR and contractility (+ve chrono- and inotropy) → ↑ C.O. - Modest β_2-related peripheral vasodilation → offset by α_1-mediated vasoconstriction (by L-isomer) at higher doses (> 5 ug/kg/min) → thus, SVR generally unchanged - ↑ BP due to ↑ C.O. (despite β_2-mediated ↓ SVR) - ↑ cardiac MRO_2 due to ↑ HR/contractility - ↑ coronary blood flow due to coronary vasodilation
GU effects	- ↑ RBF and urine output due to ↑ C.O. (not due to renal arteriolar vasodilation)
Issues and side-effects	- Tachyphylaxis with prolonged use - High doses (> 10 ug/kg/min) causes side-effects → tachycardia, arrhythmias (esp ↑ ventricular rate of AF/flutter), angina pectoris, headache and CNS effects (anxiety, restlessness) - Avoid in pts with cardiac outflow obstruction (Eg. AS, cardiac tamponade) - ↑ heat loss during anaesthesia due to blood flow redistribution to skin

(3) Dopexamine:

- Overview – Synthetic analogue of dopamine
- Presentation and dosing – Clear colourless solution of dopexamine HCl for IV (10 mg/mL) → given as IV infusion (0.5-6 ug/kg/min, titrated to effect)
- Clinical uses – Improve CO in low CO states (Eg. LVF) → maintain renal and mesenteric perfusion
- Mechanism of action – Direct-acting sympathomimetic with agonist activity at β_2 and D1 receptors (minimal activity at β_1 and D2 receptors). May also inhibit NAd reuptake. No effect on α receptors
- Pharmacokinetics – Given IV only. Cleared rapidly via by tissue uptake and metabolism (elimination $t_{1/2}$ 5-10 mins)
- Pharmacodynamic effects:

CVS	- ↑ HR and contractility (cardiac β_2 and NAd reuptake inhibition) - ↑ C.O. due to ↓ afterload (a/w β_2-mediated vasodilation) and ↑ HR/contractility
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	- ↓ BP due to ↓ SVR (β_2-mediated vasodilation) - ↑ coronary blood flow without a change in cardiac MRO_2
Respiratory	- Bronchodilation (β_2)
CNS	- ↑ CBF (due to cerebral vasodilation) - N/V due to D2 effect at CTZ
GI/GU effects	- ↑ RBF and urine output due to ↑ C.O. and renal arteriolar vasodilation - ↑ splanchnic blood flow (due to similar effects as ↑ RBF)
Issues and side-effects	- Requires CVC for IV infusion - CVS effects – Flushing, angina pectoris, arrhythmias (rare) - N/V (D2) - Tremors and headaches (β_2) - ↓ $[\text{K}^+]$ and ↑ BGL (β_2) - Avoid if uncorrected hypovolaemia, AS, HOCM or phaeochromocytoma

(IV) Synthetic Noncatecholamines:

(1) Ephedrine:

- Overview – Naturally-occurring sympathomimetic (derived from plants, but synthesised for medical use) → 4 isomers, but only L-isomer active
- Presentation and dosing:
 - o Tablet (15-60 mg) and Elixir (3 mg/ml) → PO 30 mg q8h. Onset in 60 mins, with effects lasting 3-5 hrs
 - o Nasal drops (0.5%/1%) → 1-2 drops q4h
 - o Clear colourless solution of ephedrine sulphate for IV (30 mg/mL) → 3-30 mg (titrated to response). Rapid onset with effects lasting 1 hr
- Clinical uses:
 - o (i) Treat hypotension a/w ↓ SVR due to regional or general anaesthesia
 - o (ii) Treat bronchospasm
 - o (iii) Treat nocturnal enuresis
 - o (iv) Treat narcolepsy
 - o (v) Used as a nasal decongestant
- Mechanism of action:
 - o (i) Has both direct-acting (agonist activity at α and β receptors) and indirect-acting (cause endogenous NAd release) sympathomimetic effects
 - o (ii) May also inhibit MAO metabolism of NAd
- Pharmacokinetics:

Absorption	PO, IM, S/C or IV routes
Distribution	↑ lipid soluble cf. catecholamines (↑ ability to cross BBB to cause CNS effects)
Metabolism/ Elimination	- Not metabolised by MAO or COMT; some hepatic metabolism via oxidation, demethylation, hydroxylation - Also excreted unchanged in urine (65%) - Elimination $t_{1/2}$ 4-6 hrs (due to slow metabolism/clearance)

- Pharmacodynamic effects:

CVS	- ↑ HR and myocardial contractility (β_1) → ↑ C.O. - ↑ BP (↑ SBP, DBP and MAP) due to ↑ C.O. - SVR unchanged (α_1-mediated vasoconstriction in skin, renal and splanchnic vascular beds offset β_2-mediated vasodilation in skeletal muscle) - ↑ cardiac MRO_2 (due to ↑ HR/contractility) but ↑ coronary blood flow (due to β_2-mediated coronary vasodilation)
Respiratory	- Bronchodilation (β_2) - Respiratory stimulant (↑ MV) - ↑ PAP due to ↑ PVR (α_1-mediated)

CNS and ocular effects	- ↑ CBF (due to cerebral vasodilation) - CNS stimulation (↓ MAC) - Mydriasis
GI/GU effects	- ↓ renal and splanchnic blood flow (α_1) - Relaxes pregnant uterus and ↑ uterine blood flow (β_2) - Urinary retention (bladder sphincter contracts (α_1) and detrusor relaxes (β_2))
Issues and side-effects	- Tachyphylaxis (due to depletion of NAd stores in post-ganglionic SNS nerve terminal) - Obstetrics issues – Ephedrine previously favoured to treat ↓ BP a/w neuraxial block in parturients as it did not ↓ uterine blood flow and produces similar anti-hypotensive effects cf. pure α-agonists (Eg. phenylephrine) → BUT it is a/w poorer cord gas pH and ↑ foetal acidosis - Interaction with MAOi → risk of HTN crisis - CVS issues – Can precipitate arrhythmias (esp with halothane) and excessive HTN - Unwanted CNS stimulation and ↑ anaesthetic requirements - Urinary retention (see above)

(2) Metaraminol:

- Presentation and dosing – Clear colourless solution of metaraminol tartrate (10 mg/mL) → IV bolus of 0.5-2 mg. Onset in 1-2 mins (max effect in 10 mins), lasting 20-60 mins
- Clinical uses – Treat hypotension a/w ↓ SVR due to regional or general anaesthesia
- Mechanism of action – Direct- and indirect-acting sympathomimetic effects with agonist effects on both α and β effects → mainly α_1 effect (with some β effect also)
- Pharmacokinetics:

Absorption	Available via IV route only
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)
Metabolism/ Elimination	Not metabolised by COMT or MAO

- Pharmacodynamic effects:

CVS	- ↑ BP (SBP, DBP, MAP) due to ↑ SVR (α_1-mediated peripheral vasoconstriction) - ↓ C.O. due to (i) ↑ SVR (↑ afterload) and (ii) BRR-mediated bradycardia (a/w ↑ BP) → Nb. this can be prevented with atropine - ↑ coronary BF (due to ↑ diastolic perfusion time a/w bradycardia)
Respiratory	↑ PAP (due to α_1 -mediated ↑ PVR)
CNS	↓ CBF (due to α_1 -mediated cerebral vasoconstriction)
GI/GU	- ↓ renal and splanchnic blood flow (due to α_1-mediated vasoconstriction) - Contracts pregnant uterus and ↓ uterine blood flow (α_1)
Issues and side-effects	- Extravasation → localised vasoconstriction and tissue necrosis - Rapid and large ↑ BP (afterload) can ppt acute LVF - Interaction with MAOi → risk of HTN crisis - Obstetrics issue – As effective as ephedrine at managing ↓ BP in parturients with neuraxial block and ↑ cord gas pH (↓ foetal acidosis) despite ↓ uterine blood flow. But ↑ risk of significant maternal HTN - Sudden withdrawal of use can ppt profound hypotension (due to depletion of nerve terminal NAd stores) - Chronic IVI can cause hypotension (as metaraminol is taken up by SNS nerve terminals and stored as a substitute for NAd → a weak

	“false neurotransmitter” with 10% of NAd activity)
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(3) Phenylephrine:

- Presentation and dosing – Clear colourless solution for IV (10 mg/mL) → IV bolus of 50-100 ug (rapid onset lasting 5-10 mins) or IM/SC 2-5 mg (15 mins onset but lasts 1 hr)
- Clinical uses:
 - o (i) Treat hypotension a/w ↓ SVR due to regional or general anaesthesia → Nb. it is ideal for pts with IHD or AS b/c it ↑ coronary perfusion pressure without any +ve chronotropic effect (Ie. ↑ diastolic perfusion time a/w bradycardia)
 - o (ii) Treat SVT a/w hypotension (slows HR by reflex vagal effects)
 - o (iii) Combined with LA solution (1:80-200k) to cause localised VC → ↓ systemic absorption and ↑ duration of action of LA
 - o (iv) Used as a nasal decongestant
 - o (v) Used as a mydriatic agent
- Mechanism of action:
 - o (i) Mainly direct-acting sympathomimetic with agonist activity at α_1 receptor (minimal α_2 and β receptor effects)
 - o (ii) Very minimal indirect-acting effects

- Pharmacokinetics:

Absorption	IV, IM or S/C
Distribution	Poorly lipid soluble (minimal CNS effects as it cannot cross BBB)
Metabolism/ Elimination	Metabolised in liver by MAO

- Pharmacodynamic effects:

CVS	- ↑ BP (SBP, DBP, MAP) due to ↑ SVR (α_1-mediated peripheral vasoconstriction) - ↓ C.O. due to (i) ↑ SVR (↑ afterload) and (ii) BRR-mediated bradycardia (a/w ↑ BP) → Nb. this can be prevented with atropine - ↑ coronary BF (due to ↑ diastolic perfusion time a/w bradycardia)
Respiratory	↑ PAP (due to α_1 -mediated ↑ PVR)
CNS	↓ CBF (due to α_1 -mediated cerebral vasoconstriction)
GU/GI	- ↓ renal and splanchnic blood flow (due to α_1-mediated vasoconstriction) - Contracts pregnant uterus and ↓ uterine blood flow (α_1)
Issues and side-effects	- Rapid and large ↑ BP (afterload) can ppt acute LVF - Obstetrics issue – As effective as ephedrine at managing ↓ BP in parturients with neuraxial block and ↑ cord gas pH (↓ foetal acidosis) despite ↓ uterine blood flow. But ↑ risk of significant maternal HTN - ↓ rostral spread of neuraxial block due to epidural vein constriction → ↓ EDV engorgement and epidural space pressure

(4) Methoxamine:

- Presentation and dosing – Clear colourless solution of methoxamine HCl for IV (20 mg/mL) → Given IV 1 mg/min to total dose of 5-10 mg (onset in 1-2 mins, lasting 1 hr), or IM/SC 5-20 mg (onset in 20 mins, lasting 90 mins)
- Clinical uses – (i) Treat hypotension a/w ↓ SVR due to regional or general anaesthesia, (ii) Treat SVT a/w hypotension (slows HR by reflex vagal effects)
- Mechanism of action – Direct-acting sympathomimetic with specific α_1 agonist effects
- Pharmacodynamic effects:

CVS	- ↑ BP (SBP, DBP, MAP) due to ↑ SVR (α_1-mediated peripheral vasoconstriction)
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	- ↓ C.O. due to (i) ↑ SVR (↑ afterload) and (ii) BRR-mediated bradycardia (a/w ↑ BP) → Nb. this can be prevented with atropine - ↑ coronary BF (due to ↑ diastolic perfusion time a/w bradycardia) - Direct antiarrhythmic effect (?mechanism)
Respiratory	↑ PAP (due to α 1-mediated ↑ PVR)
CNS	↓ CBF (due to α 1-mediated cerebral vasoconstriction)
GU/GI	- ↓ renal and splanchnic blood flow (due to α1-mediated vasoconstriction) - Contracts pregnant uterus and ↓ uterine blood flow (α1)
Issues and side-effects	Interaction with MAOi → risk of HTN crisis

(5) Amphetamines and related sympathomimetics (methamphetamines, dextroamphetamines):

- Similar to ephedrine in producing α and β agonist effects but differs in that it is a/w:
 - o (i) Significant CNS stimulation
 - o (ii) Appetite suppression (due to reflex NAd release from CNS storage sites)
 - o (iii) Drug dependence (due to CNS effects)
 - o (iv) Significant tachyphylaxis
- Nb – Acute use of amphetamines ↑ anaesthetic requirements (↑ NAd in CNS), while chronic use ↓ anaesthetic requirements (↓ NAd in CNS)

ASIDE: β_2 Agonists

Clinical uses of β_2 agonists:

- (i) Prevent and treat reversible AW obstruction 2° to bronchospasm (acute exacerbations of asthma/COPD)
 - o Usually given via inhaled route as MDI or nebulised (to ↓ side-effects caused by systemic absorption), but can also be given PO, S/C or via IV infusion
 - o Either – (i) Intermediate-acting (3-6 hrs) → salbutamol, terbutaline; (ii) Long-acting (> 12 hrs) → salmeterol
- (ii) “Tocolytics” → given as IV infusion to stop premature labour by ↓ uterine contractions

Mechanism of action of β_2 agonists:

- Direct-acting sympathomimetic effects on β_2 receptors

Pharmacodynamic effects of β_2 agonists:

Respiratory	- Bronchodilation due to bronchial SM relaxation - Reversal of hypoxic pulmonary vasoconstriction (↑ shunt/V/Q mismatch)
CVS effects	- ↑ HR due to (i) β_1 stimulation (esp at high-doses) and (ii) BRR-mediated response 2° to ↓ BP caused by β_2-mediated peripheral vasodilation - ↓ SVR due to β_2-mediated peripheral vasodilation → ↓ BP
GU effects	- Uterine SM relaxation
Metabolic effects	- ↓ K^+ (stimulates Na^+/K^+ ATPase activity → ↑ IC K^+ transport) - ↑ BGL (esp in DM pts) - ↑ lactate production due to β_2-mediated glycogenolysis and lipolysis
Issues and side-effects	- Tremor (due to direct β_2 stimulation of skeletal muscles) - Tachycardia (see above) and arrhythmias (esp if ↓ K^+) - Hypoxaemia (due to ↑ shunting and V/Q mismatching) - ↑ BGL (esp in DM pts) - ↓ K^+ and Mg^{2+} (see above) - Lactic acidosis (see above)

Specific types of β_2 agonists:

(1) Salbutamol:

- Clinical uses – (i) Prevent/treat reversible AW obstruction due to bronchospasm, and (ii) Stop premature labour (as a tocolytic agent)
- Presentation – Clear colourless solution for IV (50-500 ug/mL) or nebulisation (2.5-5 mg/mL), MDI (100 ug), syrup (0.4 mg/mL) or tablets (2-8 mg)
- Pharmacokinetics:

Absorption	- Poorly absorbed PO (due to ↑ hepatic first-pass metabolism) - Usually given via inhaled or IV route
Distribution	10% protein-bound. Can cross placenta
Metabolism/ Elimination	- Hepatic metabolism (to inactive 4-O-sulphate, which is excreted in urine) - Elimination $t_{1/2}$ 4-6 hrs

- Pharmacodynamic effects – See above

(2) Salmeterol:

- Long-acting β_2 agonist used to prevent reversible AW obstruction due to bronchospasm (not used acutely due to slow onset)
- Long non-polar side-chains on N-terminal amine → ↑ lipophilicity → ↑ β_2 affinity → ↑ potency (15x ↑ cf. salbutamol), ↑ duration of action (12 hrs vs 4 hrs for salbutamol), ↓ β_1 effect (4x ↓ cf. salbutamol)
- Also has anti-inflammatory effects also (prevents histamine, leukotriene and PGD₂ release from mast cells)

(3) Terbutaline:

- β_2 agonist with some β_1 activity also that is used to treat asthma and premature labour

(4) Ritodrine:

- β_2 agonist used to stop uterine contractions causing premature labour
- Given as continuous IVI (350 ug/kg/min) until uterine contractions inhibited
- Issues and side-effects:
 - o (i) Crosses placenta $\rightarrow$ foetal tachycardia, $\downarrow$ BGL (due to maternal hyperinsulinaemia), and $\downarrow$ K^+
 - o (ii) Maternal effects – Tachycardia (β_1 -mediated), pulmonary oedema with aggressive fluid hydration (due to $\uparrow$ renin $\rightarrow$ $\uparrow$ Na^+/H_2O retention), $\downarrow$ K^+ , $\uparrow$ BGL (esp in pts with DM or receiving steroid therapy for foetal lung maturation), hyperinsulinaemia, N/V, agitation/restlessness and seizure activity