AUTONOMIC SYSTEM PHARMACOLOGY

Part 1:

GENERAL CONCEPTS

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PLAN FOR LECTURES

1. General concepts
2. Sympathomimetics
3. Sympathetic blockers
4. Muscarinic drugs
5. Nicotinic drugs

Autonomic nervous system controls the visceral functions of the body, largely under involuntary control.

Divided into sympathetic and parasympathetic systems.

OVERVIEW

- Anatomical layout
- Transmitters
- Receptors
- Effects on end organs
- Drug classes
  - Cholinergic + modifiers
  - Adrenergic + modifiers

ANATOMICAL LAYOUT 1/2

Series of 2 nerves, pre & post ganglionic.

Parasympathetic Nervous System (PsNS)

- Preganglionic cell body in cranio- (III, VII, IX, X) sacral (S1-4) CNS
- Long preganglionic nerve to wall of end-organ
- Short intramural postganglionic fibre

ANATOMICAL LAYOUT 2/2

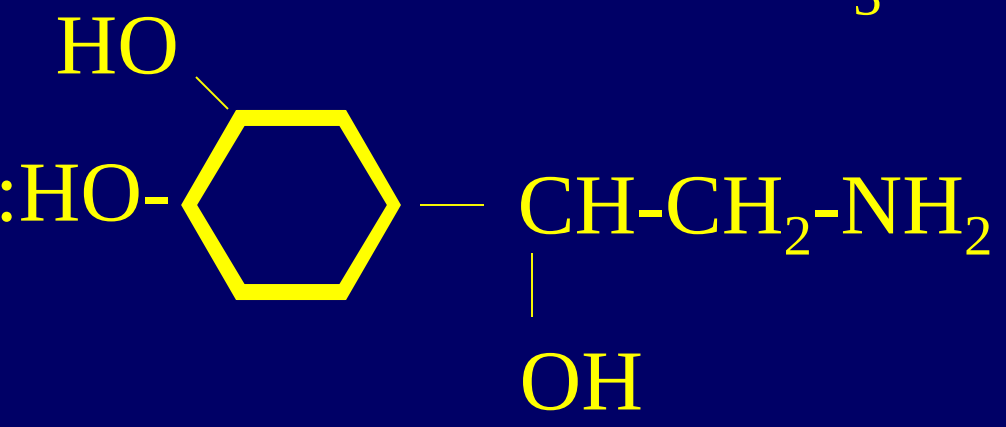
Sympathetic Nervous System (SNS):

- cell body in intermediolateral horn of thoracolumbar spinal cord (T1 to L2)
- short preganglionic nerve to ganglion *either* in paravertebral sympathetic chain *or* prevertebral ganglia to synapse with:
- long postganglionic nerve to end-organ. n.b. adrenal medulla which releases adrenaline (Adr)

TRANSMITTERS 1/3

There are two main ones:

- Acetylcholine: 
  (ACh)

- Noradrenaline: 
  (NA)

TRANSMITTERS 2/3

- All preganglionic fibres are cholinergic (ACh), both SNS & PsNS
- PsNS postganglionic neurones are also cholinergic (ACh)
- Most SNS postganglionic neurones are adrenergic (NA rather than Adr)
  - Except sweat glands, piloerector muscles & a few blood vessels which are cholinergic

TRANSMITTERS 3/3

- Both transmitters are preformed and stored in the vesicles in the nerve endings
- With depolarisation, vesicles fuse to membrane and empty contents to exterior
- They diffuse across the synapse to reach the membrane of the effector cell (post-ganglionic or end-organ)

RECEPTORS 1/3

- NA and ACh stimulate the effector organ by binding to highly specific sites on the outer cell membrane (receptors), linked to the cell interior by transmembrane proteins.

- Activation causes changes in ion permeability or enzyme activity and leads to cellular action

RECEPTORS 2/3

Cholinergic receptors are of 2 kinds, both activated by acetylcholine:

- Nicotinic

  At SNS and PsNS ganglia i.e. on postganglionic cell bodies & non-ANS sites e.g. motor end plate

- Muscarinic

  Found at all PsNS postganglionic nerve endings & SNS postganglionic cholinergic nerve endings

  i.e. on these effector cell membranes

RECEPTORS 3/3

Adrenergic receptors are of two main types which are stimulated to different extents NA & Adr:

- α-receptors
  - vasoconstriction, pupil dilation, intestinal relaxation, sphincter contraction,
- β-receptors
  - β1: +ve inotropic and chronotropic, lipolysis
  - β2: vasodilatation, intestinal, bronchial, bladder & uterine relaxation, glycogenolysis

DESTRUCTION OF TRANSMITTERS

Both are short lived after secretion across the synapse:

- Cholinergic transmission is terminated by acetylcholinesterase in the post-synaptic environment. Re-used in the presynaptic nerve ending.
- Adrenergic transmission is terminated by re-uptake into the presynaptic nerve ending (most) & by metabolism: MOA and COMT.

ADRENAL MEDULLA

A special case in the postganglionic SNS.

- Releases Adr:NA 4:1, into blood stream
- Adrenergic actions last much longer
- Adr has equal α and β activity, while NA has strong α and little, if any, β activity.

EFFECTS OF SYMPATHETIC STIMULATION

EFFECTS OF PARASYMPATHETIC STIMULATION

THE CONCEPT OF "TONE"

SNS & PsNS are continually active, the basal activity is called tone.

- Importance is that it allows a single system to alter the activity of an end-organ
  - E.g. SNS keeps arterioles constricted at half their maximum diameter
    - Increased SNS tone ⟶ vasoconstriction
    - Decreased SNS tone ⟶ vasodilatation
  - Each organ has a predominant tone, SNS or PsNS

GANGLIONIC NEUROTRANSMISSION

At the synapse between pre & post ganglionic nerve is cholinergic, to nicotinic receptors.

- Ganglion stimulants: nicotine
- Ganglion blockers: hexamethionium

  (the earliest anti-hypertensives)

DRUGS THAT ACT OF ADRENERGIC RECEPTORS

	agonist	antagonists
α_1	NA, Adr, ephedrine*, phenylephrine	Phenoxybenzamine,phentolamine, indoramin, labetolol, prazosin, doxazosin
α_2	NA, Adr, ephedrine*, clonidine, methyldopa	Phenoxybenzamine, phentolamine
β_1	Adr, ephedrine*, isoprenaline, dopamine, dobutamine	Propranolol, labetolol, timolol, atenolol, metoprolol
β_2	Adr,ephedrine*, isoprenaline, salbutamol, terbuterline, salmeterol	Propranolol, labetolol, timolol

CONCLUSION

- Anatomical layout: pre & post ganglionic nerves
- Transmitters: Ach & NA (Adr)
- Receptors: M/N & α/β
- Effects on end organs: 'fight or flight' vs 'sleepy old man'
- Drug classes:
  - Cholinergic agonists, anticholinergics, Ach-esterase inhibitors
  - Adrenergic agonists and antagonists: α and β