


I. Cholinergic [NOTE 9-2]

Nicotinic Receptor

Ganglionic stimulant: Nicotine

- Dose: small → main actions are central
larger → stimulate ganglia
larger → block ganglia (possibly by a mechanism analogous to depolarizing neuromuscular block)
- Acute effect of smoking (absorbing nicotine): CNS stimulant
↑ sym / parasympathetic activity (↑BP, tachycardia, inhibition of gastric motility etc.)
Release of antidiuretic hormone (ADH) from posterior pituitary gland)

Ganglion blocking drug: Hexamethonium: No longer used in man

(Not affecting neuromuscular transmission)
Trimetaphen: produced controlled hypotension during surgery occasionally.

- Mechanism: Either as competitive antagonists, open channel blockers or a mixture of both.
(at postsynaptic receptors) (at ligand-gated ion channels)
- Effects on: (final effects depend on whether para or sympathetic signaling predominates at the site)
 - ① Cardiovascular system (e.g. Dilatation of arterioles and veins, BP) → Block sympathetic system
 - ② Gastrointestinal tract (e.g. ↓ GI motility → Block para)
 - ③ Genito-urinary system (e.g. impairment of micturition → Block para)
 - ④ Eye: loss of accommodation

Neuromuscular blocking drug:

- Competitive blockers (Non-depolarizing curare): tubocurarine, vecuronium, pancuronium, atracurium
(related to postsynaptic receptors)

Relative long duration of action: action is reversed by cholinesterase blocker administration

- Depolarizing blocker: Suxamethonium = succinylcholine (only example in use)
(related to postsynaptic channels)

Agonist, resistant to hydrolysis by acetylcholinesterase, sustained depolarization → muscle fibre membrane after 1st AP becomes inexcitable, can be hydrolysed by butyrylcholinesterase (in plasma, rather non-specific)

- Drugs affecting other steps of ACh transmission:

Botulinum toxin: exceptionally potent, blocks release of ACh at NMJ and ganglia, no effect on postsynaptic mechanisms. It can be used for prolonged relief of muscle spasm in dystonia.

Hemicholinium: structurally similar to choline, inhibits competitively the uptake of choline by cholinergic nerve terminals by inhibiting choline uptake carrier.

Streptomycin and other aminoglycoside antibiotics: Inhibit ACh release by blocking Ca^{2+} entry.

- Cholinesterase inhibitors:

- Short-acting anti-cholinesterase: **Endrophonium**
 - Possess a quaternary ammonium group $^+$ to bind to anionic site (ionic binding)
 - No group complementary to the esteratic site.
- Medium- or long-acting anti-ChE: **Neostigmine, eserine = physostigmine**.
 - bind both sites, form an ester bond with the serine hydroxyl group.
 - Slower spontaneous hydrolysis. [Enzyme molecule inactivated for several min]
- Long-acting (or irreversible) anti-ChE: **Dyflos (DFP), parathion, esothiopate**, are organophosphat compounds.
 - Phosphorylate the serine -OH. Hydrolysis of phosphorylated enzyme is negligibly slow (may require enzyme resynthesis)
Few compounds (e.g. esothiopate) hydrolysis occurs in a few hours.
 - Effects and uses and toxicity on note

- Cholinesterase reactivators:
 - ChE following phosphorylation can be reactivated by oxime compounds. (e.g. pralidoxime), bind to the anionic site, at right distance to the phosphate group → oxime hydroxyl group substitute for the serine hydroxyl (used for treating organophosphate poisoning)

Muscarinic Receptors [Note 8-1]

- Cholinergic agonist: Acetylcholine (ACh)
 - Mechanism: - Small dose → muscarinic action (Parasymp) : Vasodilation bradycardia.
 - Large dose → nicotinic action : vasoconstriction and tachycardia (postganglionic neurons activation), Secondary action due to adrenaline released from adrenal medulla.
- Muscarinic receptor inhibitor: atropine
 - Summary of the location and function of peripheral ACh receptors on Note
 - Muscarinic receptors can be presynaptic for inhibition of NA release (Note)

Parasympathomimetic drugs can be of two types:

- { Stimulating muscarinic receptors as ACh
- As anticholinesterase

- Muscarinic agonists: (induce parasymp effects → on note)

ACh rapidly hydrolysed.

methacholine (Slow hydrolysis by ChE) **Carbachol** (No ChE hydrolysis): They are quaternary amines → fully ionized, Not absorbed when given orally, not readily absorbed from the conjunctival sac (in eyes).

Pilocarpine: tertiary amine: Partially ionized in physiological pH absorbed topically.

Bethanecho: No ChE hydrolysis: used for ↑ GI tract motility.

- Antagonist at muscarinic receptors:

Important drugs → competitive antagonists without much selectivity.

Atropine, **Hycosine**, **Homatropine**: Similar chemical structures, tertiary bases, hence enter the brain readily. (Quaternary derivatives avoid CNS effects), they block target receptors. (Effects resemble sym effects → on note: NS + PNS)

2. Adrenergic

Catecholamine (NA, AD, isoprenaline) (Note 8-3)

- Agonists of different adrenoceptors:

- NA is more potent on α -adrenoceptors than β . $\{\alpha_1: G_q \text{ coupled: PLC}$
 $\alpha_1 > \alpha_2\}$ $\{\alpha_2: G_i \text{ coupled: } \downarrow cAMP\}$
- Adrenaline (AD) is more potent on β -adrenoceptor than α . $\{\beta_1: \text{excitatory (innervated)}$
 $\beta_2: \text{inhibitory (not innervated)}$
- Isoprenaline (synthetic) very selective for β adrenoceptors.
- Phenylephrine α_1
- Clonidine α_2
- α -methyl $\alpha_2 > \alpha_1$
- Salbutamol $\beta_2 > \beta_1$

Effects of
the adrenoceptors
(NOTE → Table 2)

- Antagonists of adrenoceptors:

- Phentolamine (PHEN) α Selective ($\alpha_1 = \alpha_2$)
- phenoxybenzamine α selective
- Prazosin $\alpha_1 > \alpha_2$
- Propranolol β selective
- Atenolol $\beta_1 > \beta_2$

- Drugs treating glaucoma:
 - Dipivefrine**: (α_1 and α_2 agonist) It is more lipid soluble: produced by esterification with pivalic acid
Used to treat open-angle glaucoma by activating α_2 -adrenoceptors (Details on Note)
 - Brimonidine**: α_2 -adrenoceptor agonist for treating glaucoma (see Note)
- Indirect acting sympathomimetics.
 - Tyramine**: Displays NA in synaptic vesicles. Gets into vesicular monoamine transporter (VMAT) in exchange for NA. NA can escape via uptake 1 in exchange for NA.
 - ephedrine, amphetamine**: Act both as an indirect and a direct sympathomimetics \rightarrow cause NA release + act on post-junctional adrenoceptors.
- Adrenaline reversal:

PHEN: as an α -adrenoceptor antagonist: block the effect of AD on α -adrenoceptors. AD acting on β -adrenoceptors results in a fall in blood pressure (vasodilation)
(BP)

Drugs interfere or mimic the effects of the sympathetic nervous system.

- Ergot alkaloids: a mixture of alkaloids extracted from ergot which was the first α -adrenoceptor antagonist found.
 - { Treat migraine (ergotamine)
 - Postpartum haemorrhage (ergometrine)
 - Reversible competitive antagonist: Phentolamine (α) propranolol (β)

irreversible non-competitive: Phenoxybenzamine (D)

- Partial agonist as an antagonist for adrenoceptor:
↳ (has intrinsic sympathomimetic activity)
Oxprenolol antagonises NA
 - Drugs having effects on adrenergic neurones:

Synthesis

- Giving L-DOPA bypasses the rate-limiting step (with tyrosine hydroxylase)
 - α -methyltyrosine = Metirosine : Tyrosine hydroxylase inhibitor.
 - α -methyl dopa converted into α -methyl DA then α -methyl NA
 α -methyl NA is a false transmitter with α_2 activity
↳ (Resistant to MAO) (antihypertensive)
 - Carbidopa : Inhibits DOPA-decarboxylase.
 - Disulfiram : inhibits dopamine β -hydroxylase.

- Storage

- **reserpine**: depletion of NA by preventing the passage of catecholamines into the storage vesicles.
- **Tetrabenazine**: human vesicular monoamine transporter type 2 inhibitor (VMAT2 inhibitor)
Causing depletion of 5-HT, NA, DA from stores
(Reversible, short acting)

- Release

- **Clonidine** acting on prejunctional α_2 (NA \rightarrow auto-inhibition) (inhibits release)
- **Tyramine** displacement of NA in vesicles.
- **ephedrine & amphetamine** displacement + postjunctional adrenoceptor action.
- **Guanethidine** inhibits release: enter via uptake 1, accumulates in the sympathetic neurones. (adrenergic neuronal neurotransmission blocking agent)

- Uptake

- Uptake 1 can be inhibited by cocaine, tricyclic antidepressant - (e.g. desmethylimipramine)
- Some steroids (e.g. β -oestradiol) inhibits reuptake 2 (AD, NA gets into smooth muscle cells) \longrightarrow an extra-neuronal uptake process.

- Metabolism.
- MAO inhibitors: antidepressant phenelzine (Non-selective)
selegiline (MAO-B selective)

Smooth muscle: [Note 10-1]

- Vascular smooth muscle (VSM) stimulating agents:

NA (α₁) → Gq, PLC, InsP₃ → Ca²⁺ release

(Non-selective cation channels)

ATP as co-transmitter with NA → P_{2X} receptor: fast action
P_{2Y}: Gq coupled

Neuropeptide Y (as another co-transmitter): Mechanism unknown.

Angiotensin II: converted into from angiotensin I via angiotensin converting enzyme ACE.
ACE is inhibited by captopril. Angiotensin II acts on AT₁ receptors (G_q coupled).

endothelin (ET₁, ₂ and ₃): ET₁ derived from endothelium, acting on ET_{A,B₂}.
ET_{A,B₂} both Gq coupled.

Antagonists for ET_{A,B₂}: BQ-123, BMS 182874.

→ (also GI and uterine SM)

Vasopressin: acting on V₁ receptor to elicit VSM contraction

Analog: felypressin (V₁ selective): vasoconstrictor applied with anaesthetics.

ergot alkaloids (e.g. ergotamine): vasoconstrictor to treat migraine (a symptom of cerebral blood vessels dilation)

5-hydroxytryptamine (5-HT): 5-HT_{1D}-like receptor agonist sumatriptan constricts intracranial VSM.

- VSM relaxation:

Adrenaline: β_2

Nitrovasodilators: Releasing NO \rightarrow guanylate cyclase \rightarrow ↑cGMP in SM
Nitric oxide

phosphodiesterase (e.g. PDE-5) inhibitor: sildenafil (Viagra): PDE-5
metabolises NO, inhibition \rightarrow prolonged action.

calcium antagonist e.g. nifedipine: block voltage-gated calcium channel (VGCC)
 \hookrightarrow the dihydropyridine derivative, block L-type VGCC.

potassium channel openers

histamine (Lecture 14, H₁, H₂ receptor)

prostacyclin (Lecture 16)

- Bronchial smooth muscle:

— contraction:

ACh (M_3 muscarinic receptor) Leukotrienes C₄ and D₄

Neuropeptide A

histamine (H₁-receptor)