

Unit 2: Neurotransmission and Autonomic Pharmacology

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2.1 Neurotransmission: general aspects and steps

A **neurotransmitter** is a substance released from a nerve terminal that carries a signal across a junction to the next cell. The classical criteria are that the substance is synthesised and stored in the neuron, released by stimulation in effective amounts, reproduces the effect of nerve stimulation when applied, and has a mechanism for ending its action. Transmission at a chemical synapse runs through the same steps everywhere, and each step is a drug target:

STEPS OF NEUROTRANSMISSION AND THEIR DRUG TARGETS

- | | |
|---|--|
| 1. Synthesis of transmitter | (hemicholinium blocks choline uptake) |
| | |
| 2. Storage in vesicles | (reserpine empties amine vesicles) |
| | |
| 3. Arrival of the action potential, calcium entry | (no direct drug target in routine use) |
| | |
| 4. Release by exocytosis | (botulinum toxin prevents release) |
| | |
| 5. Action on postjunctional and prejunctional receptors | (agonists and antagonists act here) |
| | |
| 6. Termination of action uptake, metabolism or diffusion away | (acetylcholinesterase, amine uptake; anticholinesterases and SSRIs act here) |

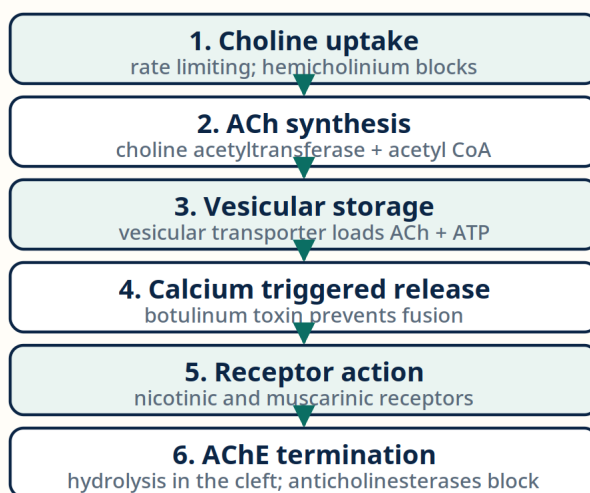
Prejunctional (autoreceptor) control makes the system self regulating: alpha2 autoreceptors on noradrenergic terminals brake further noradrenaline release (clonidine exploits this), while similar feedback exists at cholinergic and serotonergic terminals. The two great peripheral transmitters, acetylcholine and noradrenaline, are studied in detail next, exactly as the syllabus orders them.

2.2 Acetylcholine: the cholinergic transmitter

Synthesis: choline is taken up into the terminal by a high affinity sodium dependent transporter (the rate limiting step) and acetylated by **choline acetyltransferase** using acetyl coenzyme A. **Storage:** vesicles concentrate acetylcholine (ACh) with ATP by a vesicular transporter. **Release:** the action potential opens voltage gated calcium channels, calcium triggers fusion of vesicles with the membrane, and quanta of ACh enter the cleft. **Action:** ACh acts on nicotinic receptors at ganglia and the neuromuscular junction and on muscarinic receptors at effector organs (section 2.6). **Termination:** **acetylcholinesterase** in the cleft hydrolyses ACh to acetate and choline within a millisecond, one of the fastest enzymes known; the choline is recycled. Plasma butyrylcholinesterase (pseudocholinesterase) handles circulating esters, including the muscle relaxant suxamethonium, whose action is prolonged in people genetically deficient in that enzyme.

The cholinergic system divides anatomically into the parasympathetic outflow, the sympathetic cholinergic fibres (sweat glands, adrenal medulla), all autonomic ganglia, the neuromuscular junction and much of the brain, where cholinergic loss underlies the memory failure of Alzheimer disease.

The Cholinergic Synapse, Step by Step



Every step is a drug target, from synthesis to destruction.

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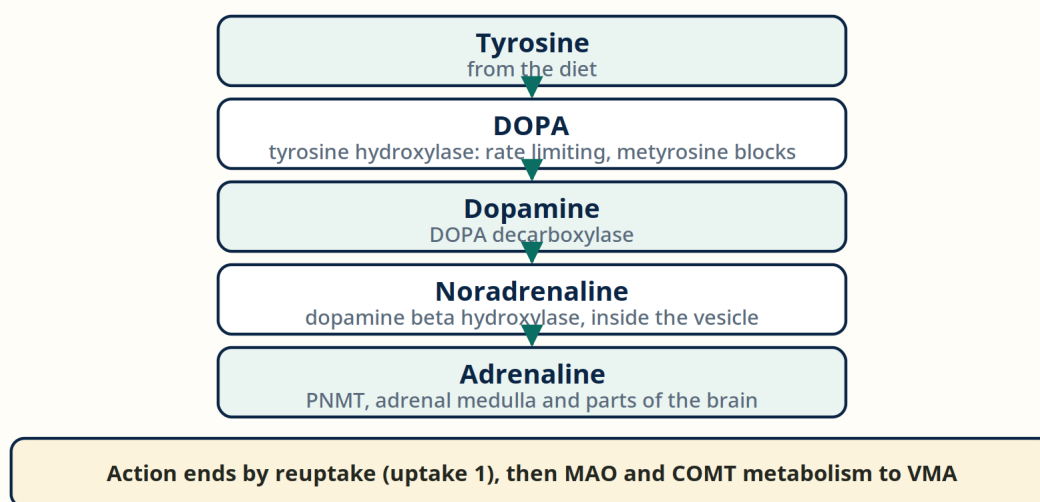
Figure: The cholinergic synapse step by step. Each step is a drug target, from choline uptake to acetylcholinesterase.

2.3 Adrenaline and noradrenaline: the adrenergic transmitters

The catecholamines are built from dietary tyrosine in a fixed sequence: tyrosine to DOPA (by tyrosine hydroxylase, the rate limiting step, inhibited by metyrosine), DOPA to **dopamine**, dopamine to **noradrenaline** (inside vesicles), and, in the adrenal medulla and parts of the brain, noradrenaline to **adrenaline** (by PNMT, an enzyme induced by cortisol draining from the adrenal cortex, a neat anatomical arrangement).

Storage and release mirror the cholinergic pattern, with VMAT pumping amines into granules (reserpine blocks VMAT and depletes them, historically an antihypertensive and a cause of depression). **Termination** differs fundamentally from ACh: there is no cleft enzyme. Action ends chiefly by **reuptake**: uptake 1, the neuronal noradrenaline transporter (blocked by cocaine and tricyclic antidepressants), returns most released noradrenaline to the terminal, where it is either restored or destroyed by mitochondrial **monoamine oxidase (MAO)**. Uptake 2 clears catecholamines into non neuronal tissues. Metabolism is by MAO and **catechol-O-methyltransferase (COMT)**, ending in vanillylmandelic acid (VMA), the urinary product once measured to diagnose pheochromocytoma. Indirect sympathomimetics such as tyramine and amphetamine work inside this machinery, displacing noradrenaline from vesicles and reversing the transporter; the tyramine "cheese reaction" in patients on MAO inhibitors, a hypertensive crisis from dietary tyramine suddenly releasing stored noradrenaline, is the system's famous toxicology.

Synthesis of the Catecholamines



No cleft enzyme: reuptake, not hydrolysis, ends the signal.

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Figure: Catecholamine synthesis from tyrosine. Tyrosine hydroxylase is rate limiting, and reuptake rather than a cleft enzyme ends the signal.

2.4 Neurotransmission in the central nervous system

The brain uses the same chemistry with a wider cast. The syllabus names six for detailed study:

Transmitter	Type	Principal receptors	Functions and pharmacology
Glutamate	Excitatory, the main CNS excitant	NMDA, AMPA, kainate, metabotropic	Learning and memory; excess causes excitotoxicity in stroke and epilepsy. Ketamine and memantine block NMDA
GABA	Inhibitory, the main CNS depressant	GABA-A (ion channel), GABA-B	Benzodiazepines, barbiturates and most anesthetics enhance it (Unit 3)
Glycine	Inhibitory, cord and brainstem	Glycine channel	Blocked by strychnine, a convulsant poison
Dopamine	Mixed, pathway dependent	D1 family (D1, D5), D2 family (D2, D3, D4)	Movement (nigrostriatal), reward (mesolimbic), prolactin control (tuberoinfundibular); the target of antipsychotics and antiparkinsonian drugs
Serotonin (5-HT)	Mixed	14 subtypes, 5-HT1 to 5-HT7	Mood, sleep, appetite, gut motility, platelet function; SSRIs, triptans, ondansetron (Unit 5)
Histamine	Excitatory in brain	H1, H2, H3, H4	Wakefulness (sedating antihistamines prove it), appetite; developed fully in Unit 5

Alongside these sit the peptide transmitters (substance P, the endogenous opioids), nitric oxide (a gas that diffuses rather than being stored), endocannabinoids (retrograde messengers made on demand) and adenosine, whose receptors caffeine blocks, the pharmacology of the world's commonest drug.

2.5 NANC transmission and cotransmission

Not every autonomic effect is adrenergic or cholinergic. **Non adrenergic non cholinergic (NANC) transmission** uses other messengers: ATP as a fast cotransmitter in the vas deferens and bladder, nitric

oxide in the gut and in penile erection (the target physiology of sildenafil), vasoactive intestinal peptide (VIP), neuropeptide Y and substance P in gut and airways.

Cotransmission is the rule that a neuron releases more than one active substance: sympathetic terminals release noradrenaline with ATP (fast contraction) and neuropeptide Y (slow, prolonged vasoconstriction), so one impulse writes a fast and a slow message. Parasympathetic terminals pair ACh with VIP in salivary glands. Cotransmission explains responses that pure adrenergic or cholinergic blockade leaves behind, and it multiplies drug targets: the purinergic P2X1 blocker, the NK1 antagonist aprepitant (an antiemetic) and CGRP pathway drugs in migraine all grew out of NANC pharmacology.

2.6 The autonomic nervous system as a drug target

The systemic pharmacology of the syllabus begins with the autonomic system. Its two divisions usually oppose each other, with clear exceptions:

Feature	Sympathetic	Parasympathetic
Outflow	Thoracolumbar (T1 to L2)	Craniosacral (III, VII, IX, X and S2 to S4)
Preganglionic fibre	Short	Long
Postganglionic fibre	Long	Short
Main transmitter at ganglia	Acetylcholine (nicotinic Nn)	Acetylcholine (nicotinic Nn)
Postganglionic transmitter	Noradrenaline (ACh at sweat glands and adrenal medulla)	Acetylcholine
Effector receptors	Alpha1, alpha2, beta1, beta2, beta3	Muscarinic M1 to M5
Dominant role	Stress response: heart rate and force up, bronchodilation, mydriasis, glycogenolysis	Rest and digest: heart slowed, gut and bladder active, miosis, salivation

The receptor map is the clinical content. Alpha1 (Gq) constricts vessels and the radial muscle of the iris; alpha2 (Gi) is prejunctional and inhibitory; beta1 (Gs) drives the heart and renin release; beta2 (Gs) relaxes bronchi, vessels and uterus; beta3 acts in fat and bladder (mirabegron). Muscarinic M1 sits in glands, CNS and gastric parietal pathways, M2 slows the heart, and M3 contracts smooth muscle and drives secretion. Every autonomic drug in sections 2.7 to 2.12 is a key turned in one of these locks.

The Two Autonomic Divisions Compared

SYMPATHETIC	PARASYMPATHETIC
Outflow	
thoracolumbar T1 to L2	craniosacral III, VII, IX, X, S2 to S4
Postganglionic transmitter	
noradrenaline (ACh at sweat glands)	acetylcholine
Effector receptors	
alpha1, alpha2 beta1, beta2, beta3	muscarinic M1 to M5
Dominant role	
stress: heart up, bronchi open, pupils wide, fuel mobilised	rest and digest: heart slow, gut and bladder active
Both divisions share one ganglion transmitter: acetylcholine at nicotinic Nn receptors.	

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Figure: The two autonomic divisions compared, outflow, transmitter, receptors and dominant role side by side.

2.7 Parasympathomimetics: cholinomimetic drugs

Drugs that mimic ACh divide into direct agonists and indirect anticholinesterases.

Direct agonists. Choline esters are resistant to hydrolysis by design: **bethanechol** (muscarinic, used for urinary retention and gut atony, given orally or subcutaneously, never intravenously), **carbachol** (mixed muscarinic and nicotinic, now mainly intraocular for miosis) and **methacholine** (a bronchial challenge test agent). The alkaloid **pilocarpine** (M3) constricts the pupil and lowers intraocular pressure in glaucoma and stimulates salivary secretion in dry mouth; **cevimeline** is a related oral sialogogue. The pattern of muscarinic effects is worth memorising as a system: miosis and accommodation for near vision, salivation and gut activity up, bronchoconstriction, bradycardia, bladder contraction, sweating. Its toxic version is the SLUDGE picture of cholinergic excess (salivation, lacrimation, urination, defecation, gastrointestinal cramps, emesis).

Anticholinesterases are covered as their own class next, since they dominate the clinical use of this area.

2.8 Anticholinesterases and organophosphate poisoning

By inhibiting acetylcholinesterase, these drugs let endogenous ACh accumulate at every cholinergic junction. They divide by chemistry and duration:

- **Reversible, short acting:** edrophonium (historically the diagnostic test for myasthenia gravis).
- **Reversible, medium acting carbamates:** **physostigmine** (tertiary amine, enters the brain; the antidote for atropine and tricyclic poisoning), **neostigmine** and **pyridostigmine** (quaternary, kept peripheral; used in myasthenia gravis and to reverse neuromuscular blockade), and the Alzheimer drugs **donepezil**, **rivastigmine** and **galantamine**, which cross into the brain to support its failing cholinergic system.

- **Irreversible organophosphates:** insecticides (parathion, malathion) and nerve gases (sarin). They phosphorylate the enzyme permanently; the bond then **ages**, becoming unbreakable.

Clinical uses span myasthenia gravis (the autoimmune destruction of nicotinic receptors, compensated by raising cleft ACh), postoperative ileus and urinary retention, reversal of muscle relaxants, glaucoma (older agents) and Alzheimer disease. **Organophosphate poisoning** combines muscarinic excess (miosis, salivation, bronchospasm, bradycardia and diarrhoea), nicotinic effects (fasciculations then paralysis) and CNS effects (confusion, convulsions, coma). Treatment is a model of applied pharmacology: **atropine** in large, escalating doses blocks the muscarinic syndrome, and the oxime **pralidoxime** reactivates the enzyme if given before ageing; benzodiazepines control the seizures. Atropine does nothing for the paralysis, which is why the oxime and ventilation matter.

2.9 Parasympatholytics: antimuscarinic drugs

Atropine, the prototype from *Atropa belladonna*, blocks all muscarinic subtypes non selectively and competitively. Its effects are the photographic negative of section 2.7: mydriasis and cycloplegia (loss of accommodation), dry mouth and dry, hot skin, tachycardia, urinary retention, constipation, reduced bronchial secretion and CNS excitation at high doses. Atropine poisoning ("dry as a bone, red as a beet, mad as a hatter, hot as a hare") is reversed by physostigmine, the one anticholinesterase that reaches the brain.

The class has been refined by selectivity and by charge. Quaternary compounds (**ipratropium** and **tiotropium** inhaled for airways disease, **glycopyrrolate** for secretions and bradycardia without CNS effects) stay out of the brain. **Hyoscine (scopolamine)** crosses into the CNS and is the best drug for motion sickness. Selective members include **pirenzepine** (M1, peptic ulcer, now historical), **oxybutynin**, **tolterodine** and **darifenacin** (M3 emphasis, overactive bladder), **tropicamide** (short mydriasis for examination), **benztropine** and **trihexyphenidyl** (anticholinergic antiparkinsonian drugs) and the bronchodilator and antisecretory uses scattered through clinical practice. Their shared adverse burden, dry mouth, constipation, urinary retention, confusion in the elderly, is the reason anticholinergic load is now counted as a prescribing risk in older patients.

2.10 Sympathomimetics: adrenergic agonists

Sympathomimetics are read straight off the receptor map of section 2.6:

Drug	Receptor profile	Main uses
Adrenaline	Alpha1, alpha2, beta1, beta2	Anaphylaxis (the life saving drug), cardiac arrest, added to local anesthetics, open angle glaucoma (older use)
Noradrenaline	Alpha1, beta1, little beta2	Septic and cardiogenic shock, to restore vascular tone
Dopamine	D1 and D2, then beta1, then alpha1 with rising dose	Shock; the dose dependent receptor recruitment is the teaching point
Dobutamine	Beta1 predominant	Cardiogenic shock and acute heart failure, inotropy with less vasoconstriction
Phenylephrine	Alpha1	Nasal decongestant, mydriatic, raises blood pressure, reflex slowing of a fast heart in SVT
Salbutamol, terbutaline	Beta2 selective	Asthma and COPD, premature labour (older use)
Clonidine, methyl dopa	Alpha2 agonists (central)	Hypertension (Unit 4); clonidine also in withdrawal states and ADHD

Drug	Receptor profile	Main uses
Amphetamine group	Indirect, release noradrenaline	ADHD and narcolepsy (methylphenidate, lisdexamfetamine)

Direct agonists bind the receptor themselves; **indirect** agents (tyramine, ephedrine in part, amphetamines) release stored noradrenaline and fade with repetition as stores empty (tachyphylaxis). Mixed agents such as ephedrine do both. The adverse effects are the physiology exaggerated: tachycardia and arrhythmias, hypertension, tremor and hyperglycaemia with beta2 drugs, and, for adrenaline given in error at high dose, hypertensive crisis; beta blockers are the antidote class, with the caveat that blocking beta receptors while alpha stimulation continues (cocaine toxicity) is itself debated territory.

2.11 Sympatholytics: adrenergic antagonists

Alpha blockers. Non selective phenoxybenzamine (irreversible) survives in one niche, preparing a phaeochromocytoma patient for surgery, where alpha blockade must precede any beta blockade. Selective alpha1 blockers (**prazosin, doxazosin, terazosin**) treat hypertension and, more durably, the urinary symptoms of prostatic enlargement by relaxing bladder neck smooth muscle; their signature adverse effect is first dose postural hypotension. **Tamsulosin** favours the alpha1A subtype of the prostate and spares blood pressure. Alpha2 antagonists such as yohimbine are of mainly historical and research interest.

Beta blockers are among the most prescribed drugs in the world and are developed fully in Unit 4; here the pharmacology is set. They divide by beta1 selectivity (metoprolol, atenolol, bisoprolol are cardioselective, a relative and dose dependent property), by intrinsic sympathomimetic activity (pindolol, acebutolol partially stimulate while blocking), by membrane stabilising activity (propranolol at high concentrations), by added alpha blockade (labetalol, carvedilol) and by additional actions (nebivolol releasing nitric oxide, sotalol blocking potassium channels). Their dangers follow their receptors: bronchospasm in asthma (beta2), masking of hypoglycaemia warning signs in diabetes, bradycardia and heart block, cold extremities, and rebound events on abrupt withdrawal from the up regulated receptor population of section 1.11.

Ganglion blockers (hexamethonium, mecamylamine) block nicotinic Nn receptors in both divisions at once; the resulting chaos of simultaneous sympathetic and parasympathetic failure retired them from practice, and they remain as a teaching demonstration that ganglia are the crossroads of the whole autonomic system.

2.12 Agents affecting the neuromuscular junction

Skeletal muscle is reached through the somatic motor nerve, whose transmitter is ACh acting on muscle type **nicotinic (Nm) receptors**. Two families of blockers paralyse by opposite logic:

- **Non depolarising (competitive) blockers:** tubocurarine historically, and the modern **atracurium, vecuronium, rocuronium and pancuronium**. They occupy the receptor without opening it; the block is surmountable, and anticholinesterases such as neostigmine reverse it by raising cleft ACh. Rocuronium also has a designed antidote, **sugammadex**, which encapsulates it.
- **Depolarising blockers: suxamethonium (succinylcholine)** agonises the receptor and holds the end plate depolarised; fasciculations precede a flaccid paralysis that anticholinesterases cannot reverse (they worsen it). It is very short acting because plasma cholinesterase destroys it, which fails in patients with atypical enzyme, and it can trigger malignant hyperthermia in susceptible patients, treated with dantrolene, and dangerous potassium release in burns and denervation injuries.

Centrally acting relaxants are a different family altogether (baclofen, a GABA-B agonist; tizanidine, an alpha2 agonist; dantrolene, blocking calcium release from the sarcoplasmic reticulum) and are used for

spasticity rather than surgical paralysis. Botulinum toxin, which prevents ACh release from terminals, completes the junction's pharmacology: a poison turned therapy for spasticity, dystonia, hyperhidrosis and chronic migraine.

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