جامعة الملك سعود
King Saud University

Pharmacology 435 team

Flash Cards

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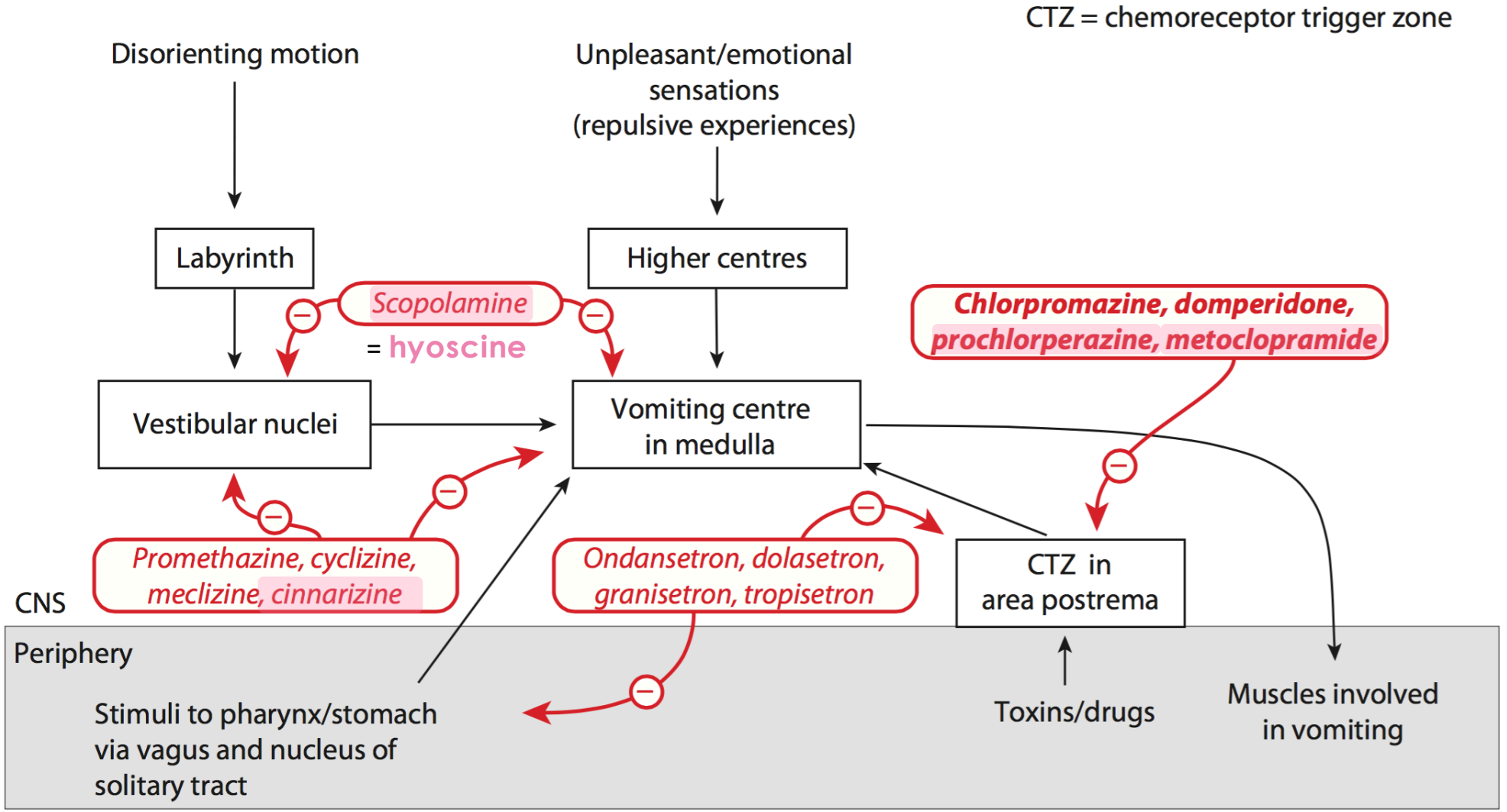
14.12 **GIT drugs** **Antiemetics** What other groups of drugs have useful antiemetic action?

The central control of vomiting and stimuli resulting in emesis



Lecture #1 | Medication affecting the balance system

Muscarinic-receptor antagonist

Scopolamine

Actions Antiemetic. Other actions consistent with antagonism of parasympathetic nervous system (see card 1.03).

MOA Reversible competitive antagonism of muscarinic receptors. Antiemetic effects due to blockade of receptors in vestibular nucleus and in the vomiting centre.

Abs/Distrib/Elim Active orally ($t_{1/2}$ 5h). A transdermal patch applied behind ear is particularly effective, lasting for up to 3 days.

Clinical use Particularly effective, when given prophylactically, against motion sickness. No efficacy against chemotherapy-induced emesis mediated via the CTZ. Effective against local gut stimuli.

Adverse effects Drowsiness. Amnesia. Actions attributable to muscarinic receptor block (dry mouth, tachycardia, blurred vision, urinary retention). Avoid in closed-angle glaucoma.

R&D 7e Ch 29, p 366; D&H 2e Ch 27, p 67

Dopamine D_2-receptor antagonist (Similar drugs: domperidone, prochlorperazine, metoclopramide thiethylperazine)

Chlorpromazine

Actions Antiemetic. Antipsychotic (see card 23.01).

MOA Reversible competitive antagonism of dopamine D_2 receptors in CTZ. Some of the side effects are due to antagonism of other receptors (e.g. adrenoceptors and histamine receptors).

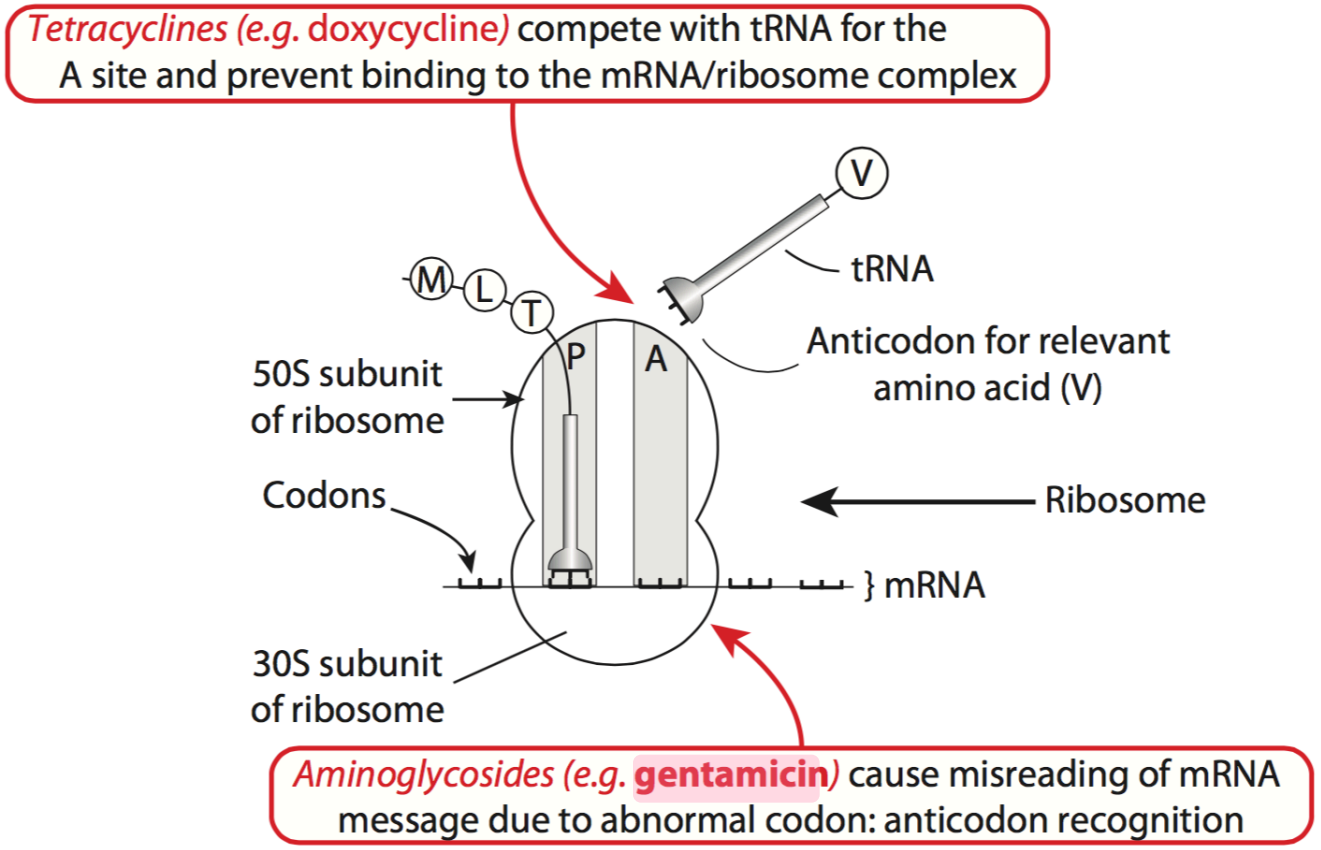
Abs/Distrib/Elim Oral administration. $T_{0.5}$ 15–30h. (P450 metabolism in liver.)

Clinical use Nausea and vomiting associated with cancer chemotherapy, radiation therapy and general anaesthesia.

Adverse effects Extrapyramidal effects – Parkinsonian symptoms (avoid in patients with Parkinson's disease). Prolactin release – galactorrhoea. Sedation. Hypotension. Antihistamine and antimuscarinic actions (e.g. dry mouth).

R&D 7e Ch 29, p 367; D&H 2e Ch 27, p 67

Bacterial protein synthesis and the antibiotics that act thereon



The ribosome moves along the messenger RNA (mRNA) which has been transcribed from DNA. Codons pass along the ribosome from the A site to the P site. A transfer RNA (tRNA) with growing peptide chain is in the P site. The incoming tRNA carries valine (V).

A bactericidal aminoglycoside antibiotic

Gentamicin

Actions Inhibits bacterial protein synthesis.

MOA Causes misreading of the mRNA message due to abnormal codon:anticodon recognition with the production of abnormal proteins.

Abs/Distrb/Elim Given i.m. or by slow i.v. injection or infusion. Can be given intrathecally. Renal excretion.

Clinical use Infections with staphylococci (with a β-lactam antibiotic), streptococci, enterococci, Gram-negative bacilli (including *P. aeruginosa*). Used for septicaemia, meningitis, pyelonephritis, endocarditis, pneumonia.

Adverse effects Dose-related ototoxicity and nephrotoxicity. GIT disturbances, rash, blood disorders can occur; ↑ototoxicity with loop diuretics; ↑effect of neuromuscular blockers.

Special points Serum levels should be monitored.

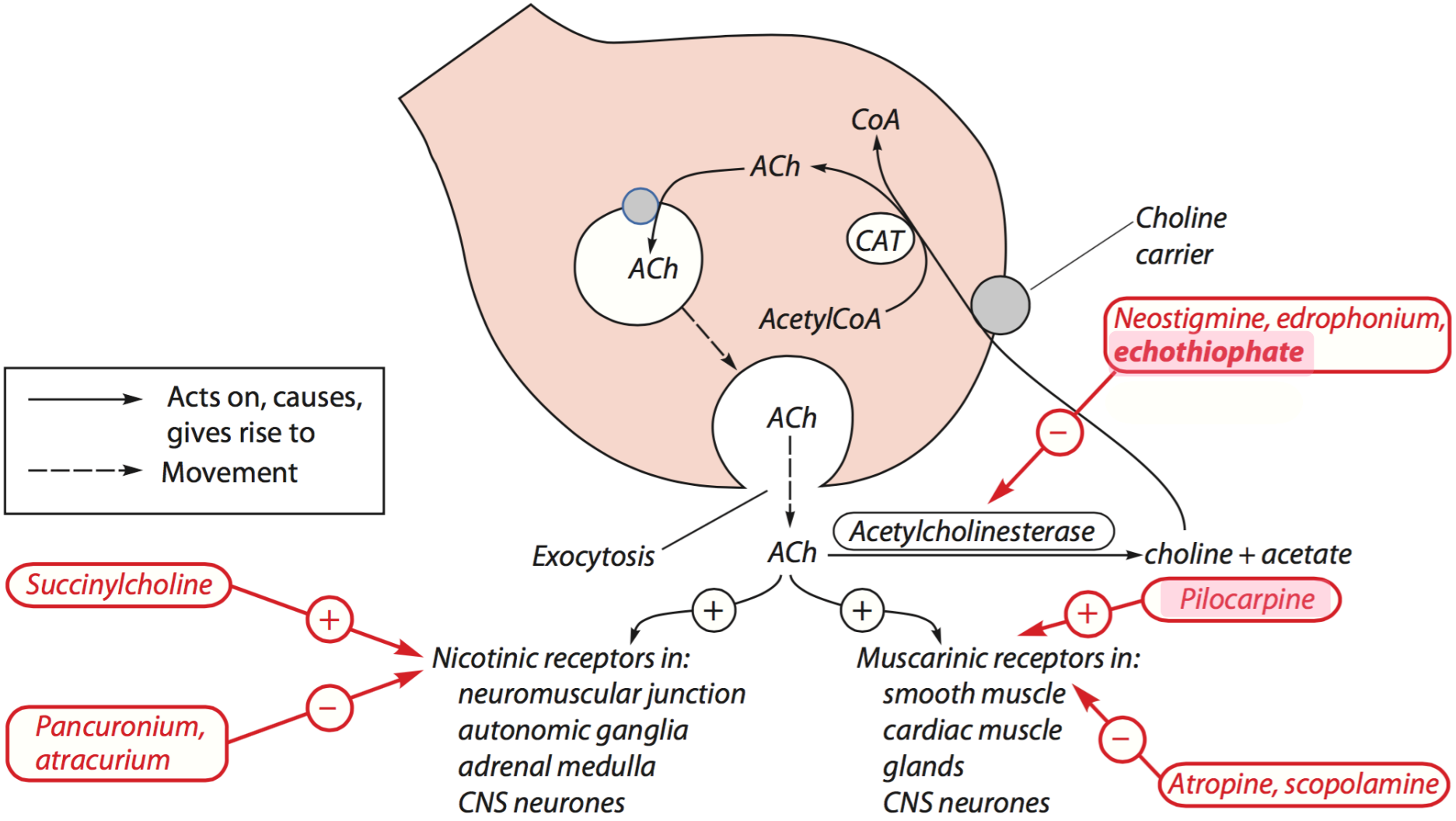
Similar drugs: Amikacin, tobramycin.

R&D 7e Ch 50, p 630; D&H 2e Ch 47, pp 108-110

Lecture #2 | Drugs acting on the eye

1.10 Summary — Cholinergic pharmacology

Simple figure of cholinergic transmission with potential sites of drug action



A muscarinic receptor agonist (Similar drug: bethanechol)

Pilocarpine

Actions Parasympathomimetic actions: contracts smooth muscle (e.g. gut, bladder, pupil); decreases rate and force of heart beat; glandular secretion (e.g. salivary, sweat, gastric acid); inhibits neurotransmitter release.

MOA Action in glaucoma is due to interaction with M_3 receptors which couple to G_q to increase cellular IP_3 and DAG concentrations. Constriction of pupil aids drainage of aqueous humour and lowers intraocular pressure.

Abs/Distrb/Elim For glaucoma pilocarpine is given as eye drops and actions last for a day. A slow delivery system placed under the eyelid acts for several days.

Clinical use Glaucoma (narrow and wide angle). Bethanechol to stimulate bladder emptying or to improve gut motility.

Adverse effects Blurred vision (contraction of ciliary muscle). Otherwise few unwanted effects because of very limited systemic absorption of topically applied drug. Bethanechol may produce bronchoconstriction.

R&D 7e Ch 13, pp 157-158; D&H 2e Ch 10, pp 28-31

Irreversible (organophosphate) anticholinesterase (Similar drugs: dyflos, sarin)

Echothiophate

Actions Parasympathomimetic – increased peristalsis, increased secretions, bradycardia, bronchoconstriction, decreased intraocular pressure. At the neuromuscular junction – fasciculation and increased twitch tension. With nerve gases (e.g. sarin) persistent potentiation of ACh action leads to paralysis and death.

MOA Irreversible inhibition of acetylcholinesterase potentiates actions of released ACh at cholinergic nerve-endings. Binds to enzyme's esteratic site causing irreversible phosphorylation. (Pralidoxime, a cholinesterase reactivator, can reverse the phosphorylation.)

Abs/Distrb/Elim Most are readily absorbed through the skin, gut and lungs. (Protective clothing needed to avoid absorption of insecticides and nerve gases.) Long-acting.

Clinical use Glaucoma.

Adverse effects May exacerbate asthma. Unwanted parasympathomimetic actions can be reduced by atropine (1.02).

R&D 7e Ch 13, pp 168-170; D&H 2e Ch 10, pp 28-31

Muscarinic receptor antagonist (Similar drugs: dicycloverine, oxybutinin, tropicamide)

Atropine

Actions Inhibits secretions (salivary, bronchial, sweat, gastric acid, etc.). Tachycardia. Relaxes smooth muscle (causing inhibition of peristalsis, pupillary dilation, paralysis of accommodation, etc.). Antiemetic (CNS effect).

MOA Competitive reversible antagonism at all muscarinic receptors.

Abs/Distrb/Elim Given orally. Half-life 3h.

Clinical use Paralysis of accommodation and pupil dilation for eye examination (tropicamide). Urinary incontinence (oxybutinin). Irritable bowel syndrome (dicycloverine). Antidote for anticholinesterase poisoning. Treatment of cardiac slowing.

Adverse effects Constipation, hyperthermia (reduced sweating), dry mouth, urinary retention, blurred vision, raised intraocular pressure, CNS excitement (delerium, hallucinations).

R&D 7e Ch 13, pp 159-160; D&H 2e Ch 10, pp 28-31

Muscarinic receptor antagonist (Similar drug: atropine)

Scopolamine

Actions Inhibits secretions (salivary, bronchial, sweat, gastric acid etc.). Tachycardia. Relaxes smooth muscle (causing inhibition of peristalsis, pupillary dilation, paralysis of accommodation etc.). CNS actions: antiemetic, amnesic.

MOA Competitive reversible antagonism at all muscarinic receptors.

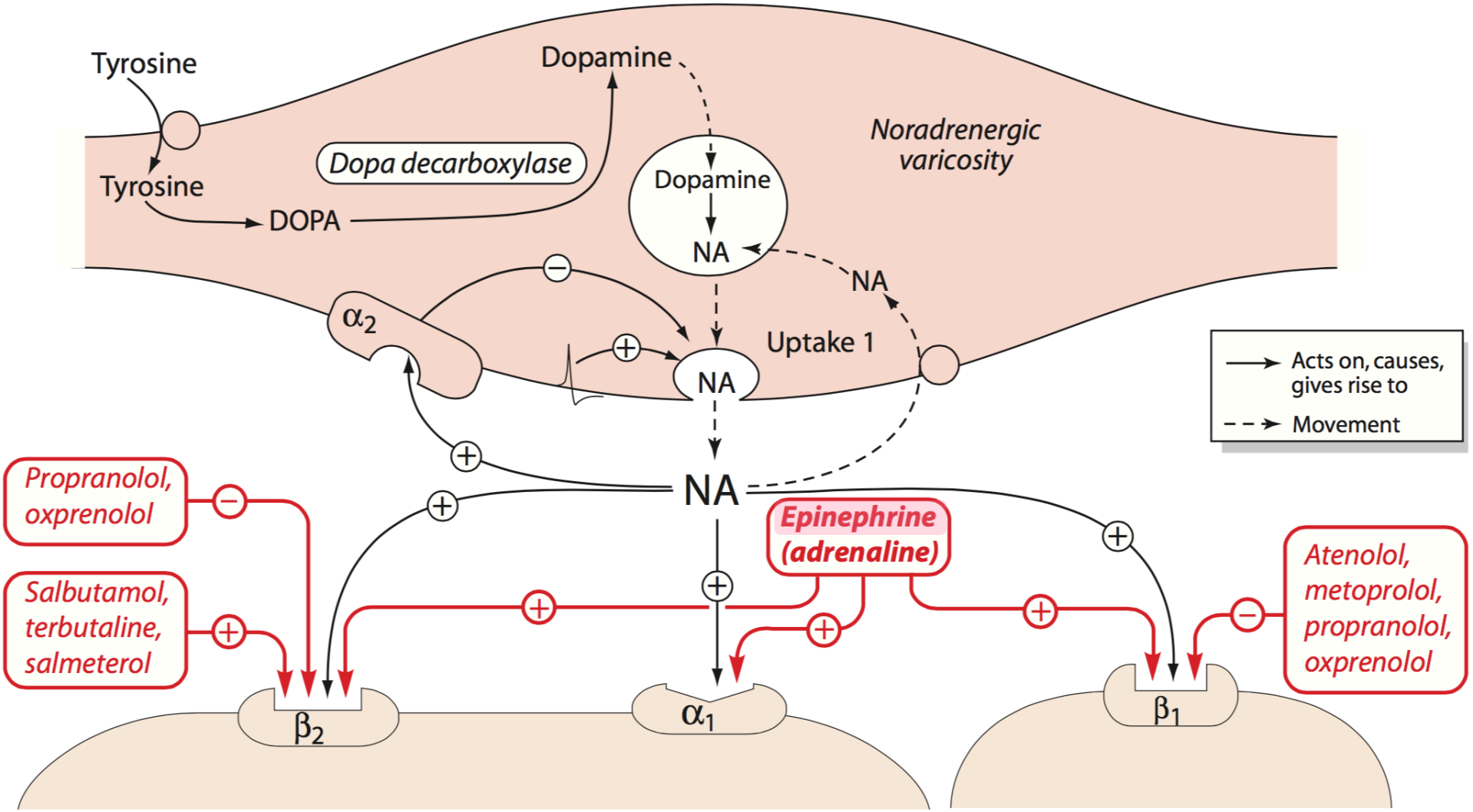
Abs/Distrb/Elim Oral admin. $T_{0.5}$ 4h. Also administered as transdermal patch for effects lasting 2–3 days.

Clinical use Main use is in motion sickness. Adjunct for anaesthesia (amnesia, inhibition of secretions and of bronchoconstriction, reduction of post-operative vomiting). Urinary incontinence.

Adverse effects Constipation, dry mouth, urinary retention, blurred vision, raised intraocular pressure, drowsiness.

R&D 7e Ch 13, pp 159-160; D&H 2e Ch 10, pp 28-31

The figure gives a simple outline of noradrenergic transmission



Agonist at α- and β-receptors

Epinephrine

Actions α_1: vasoconstriction (thus ↑BP); contraction of uterus, GIT sphincters, bladder sphincter, radial iris muscle.
α_2: inhibition of lipolysis, inhibition of NA release.
β_1: increased heart rate; β_2: bronchodilation, vasodilation with decrease in diastolic blood pressure.

MOA At α_1-receptors: Activation of phospholipase C with generation of IP_3 (which increases intracellular calcium and thus force of contraction).
At β_2-receptors: increase cAMP activates protein kinase A. In smooth muscle PKA reduces the contractile action; in cardiac muscle it increases intracellular calcium and thus the force of the contraction.

Abs/Distrb/Elim Given i.m. or s.c. Plasma $t_{½}$ 2min. Metabolised by monoamine oxidase and catechol-O-methyl transferase.

Clinical use Asthma, anaphylactic shock, cardiac arrest. Also added to local anaesthetic solutions.

Adverse effects Tachycardia, raised BP, anxiety.

Special points Phenylephrine and oxymetazoline are similar drugs except that they are α_1-selective

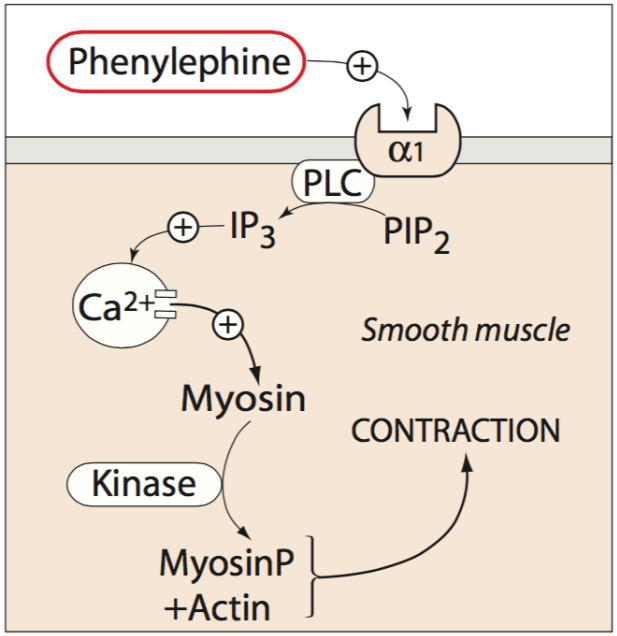
R&D 7e Ch 14, p 174; D&H 2e Ch 11, pp 32-35

An α_1-receptor agonist (Similar drugs: oxymetazoline, xylometazoline)

Phenylephrine

Actions Vasoconstriction; nasal decongestion; dilatation of pupil without effect on accommodation.

MOA Causes release of calcium from the sarcoplasmic reticulum. The increased calcium activates the contractile mechanism.



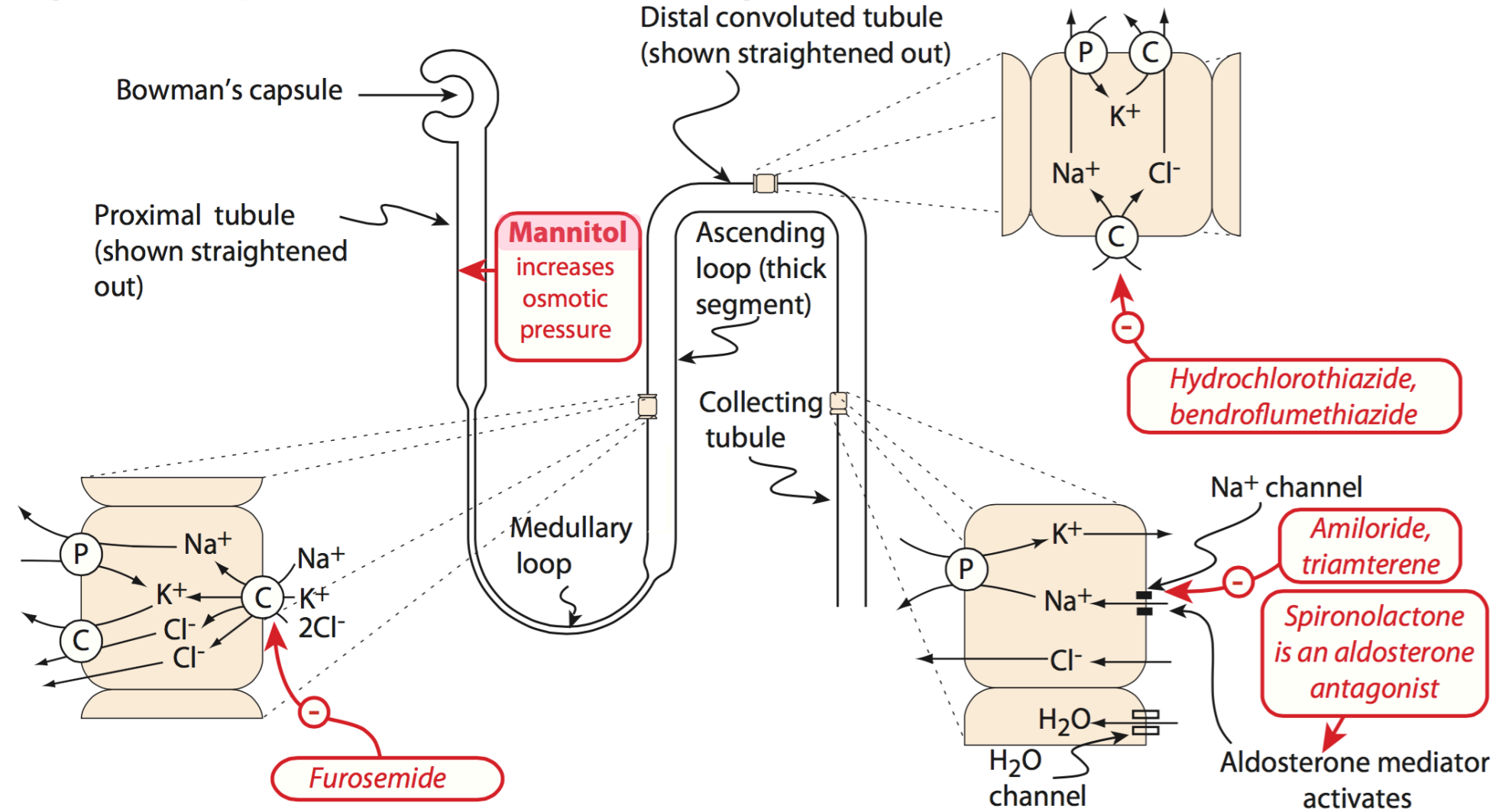
Abs/Distrb/Elim Given intranasally or topically in the eye, plasma half-life 3h, (longer in the elderly).

Clinical use As nasal decongestant; for opthalmoscopy.

Adverse effects Hypertension, reflex bradycardia.

R&D 7e Ch 14, pp 182t-184t; D&H 2e Ch 11, pp 32-35

Diagram of the nephron with 3 tubular cells shown enlarged



Osmotic diuretic

Mannitol

Actions Increases the amount or water excreted by the kidney; has a smaller effect on sodium excretion.

MOA It is an inert compound that passes across into the filtrate at the glomerulus and is not resorbed. Acts in those parts of the nephron that are freely permeable to water.

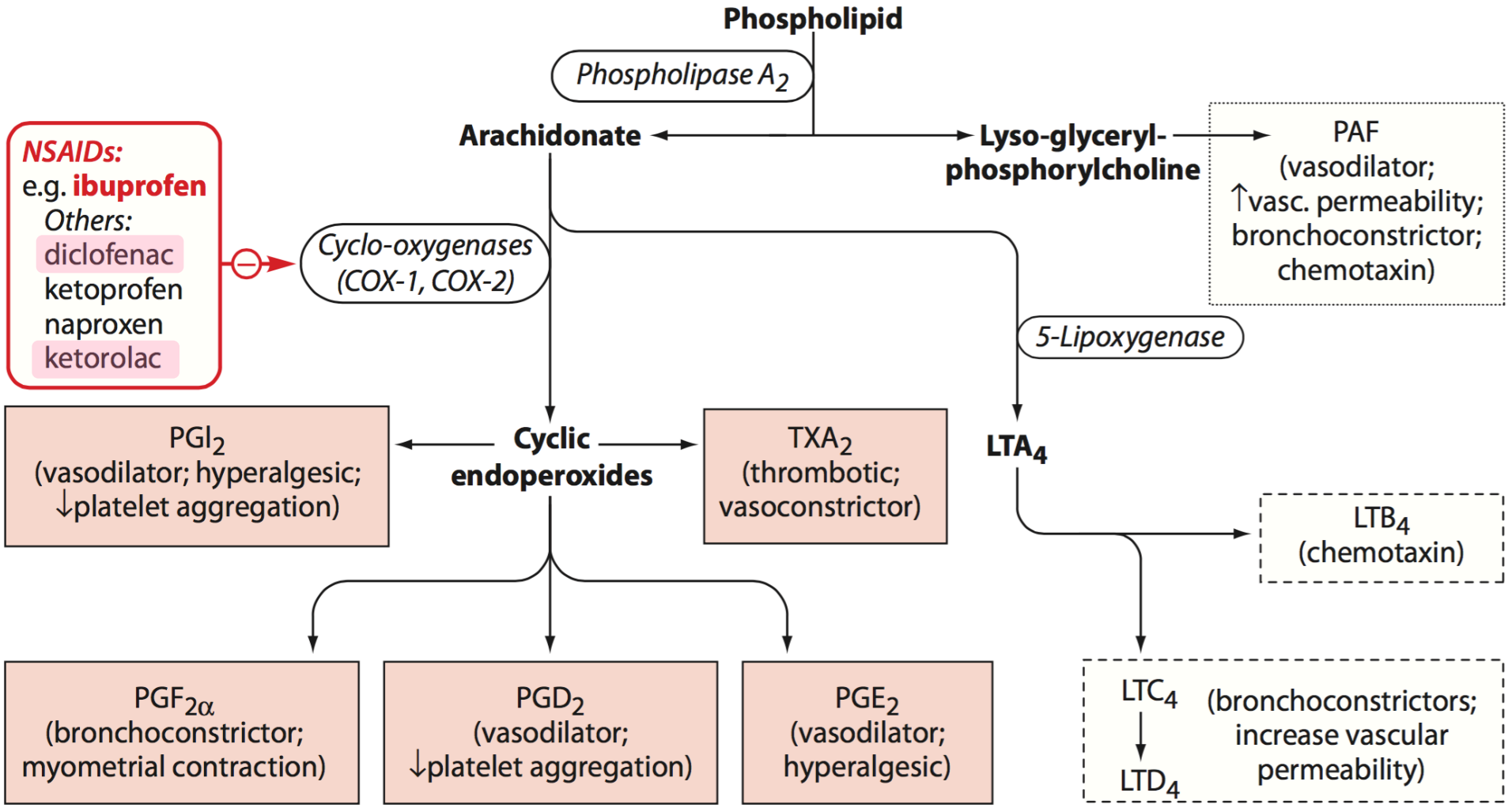
Abs/Distrb/Elim Given intravenously, not metabolised, excreted in about 30min.

Clinical use Cerebral oedema; increased intraocular pressure.

Adverse effects Temporary expansion of the extracellur fluid compartment and hyponatraemia due to osmotic extraction of intracellular water. Pulmonary oedema may occur.

R&D 7e Ch 28, p 356; D&H 2e Ch 26, pp 64-65

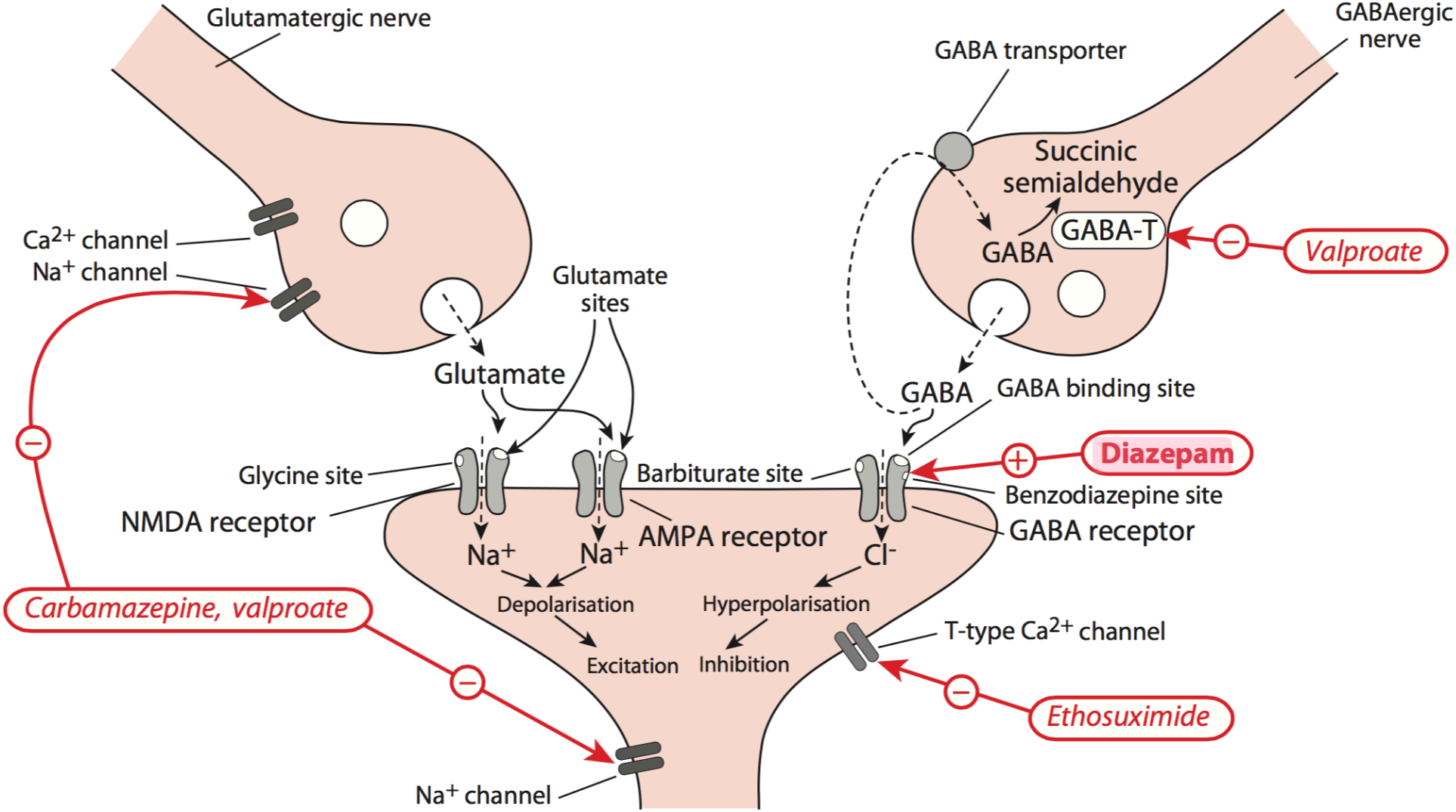
Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)



CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide* and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

Lecture #3 | Alcohol and the brain

Potential sites of action of antiepileptic drugs



Benzodiazepine (Similar drugs: clonazepam, clobazam)

Diazepam

Actions Anticonvulsant. Also hypnotic and anxiolytic (see set 22).

MOA Interacts with benzodiazepine binding site on $GABA_A$ receptor to enhance channel opening by GABA. Increased Cl^- permeability reduces electrical excitability. Clonazepam and clobazam said to be more selective anticonvulsants with less sedation.

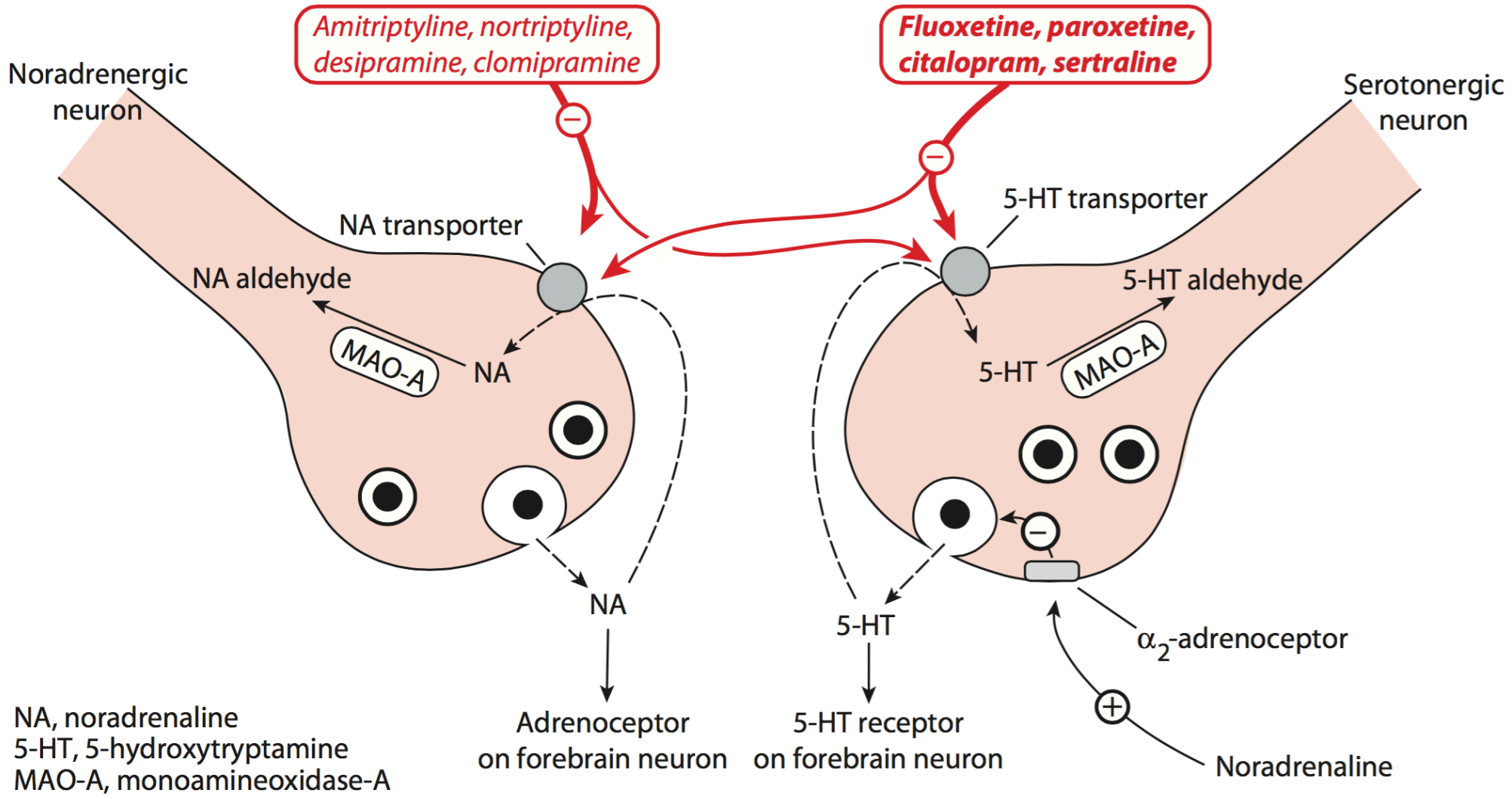
Abs/Distrib/Elim Given orally (i.v. for status epilepticus). Active metabolite of diazepam has a longer half-life (60h) and contributes significantly to actions. Metabolised by P450 system and glucuronide conjugation.

Clinical use Diazepam given i.v. for status epilepticus. Clonazepam used for tonic-clonic and absence seizures. Clobazam as an adjunctive anticonvulsant. Tolerance to anticonvulsant activity develops.

Adverse effects Benzodiazepines are safe drugs. Unwanted effect in treating epilepsy is sedation. Severe respiratory depression in combination with other CNS depressants (e.g. alcohol).

R&D 7e Ch 44, p 548; D&H 2e Ch 41, pp 94-95

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Selective serotonin reuptake inhibitor (SSRI) (Similar drugs: paroxetine, citalopram, escitalopram, sertraline, fluvoxamine)

Fluoxetine

Actions Antidepressant.

MOA Inhibits the reuptake 5-HT into serotonergic neurons, so potentiating transmitter action. The antidepressant action is not seen for a few weeks, because longer-term changes (e.g. down-regulation of receptors) are required for this. (Less marked antimuscarinic and antihistaminergic actions than the TCAs.)

Abs/Distrib/Elim Oral administration. Brain concentration rises over a few days. Hepatic P450 metabolism followed by conjugation reactions. $T_{0.5}$ 1–3 days. Longer-lasting active metabolite. (Half-lives of other SSRIs: paroxetine, 18–24h, fluvoxamine, 18–24h, escitalopram, 24–36h, sertraline, 24–36h.) Strongly bound.

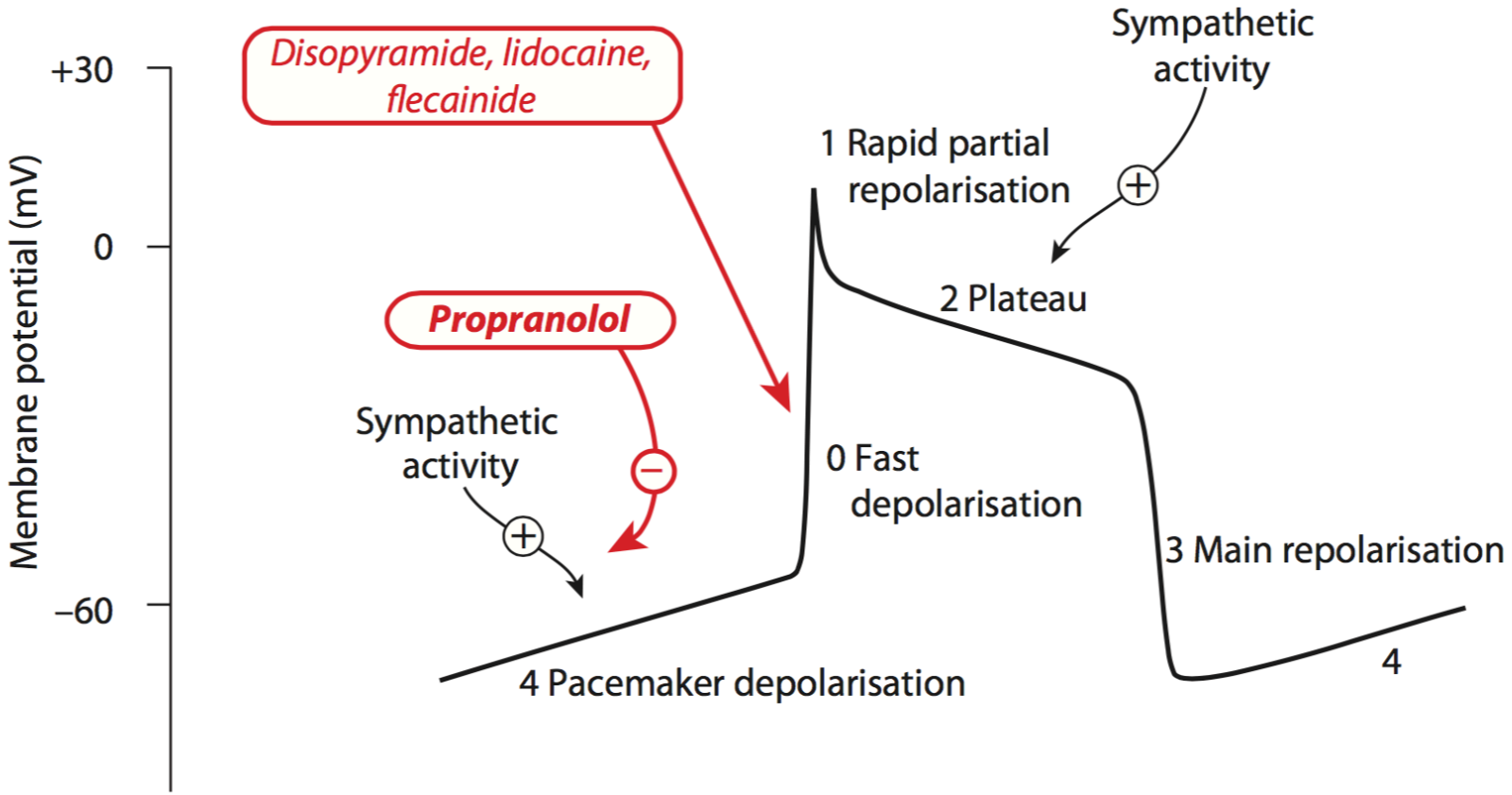
Clinical use Widely prescribed. Depression. Obsessive–compulsive disorder. Panic disorder. Bulimia nervosa.

Adverse effects Anxiety and insomnia; can cause nausea, diarrhoea and headache. Sexual dysfunction. Increased risk of suicide in young patients. Not prescribed with MAOIs (risk of serotonin syndrome). Hyponatraemia in elderly. Overdose toxicity much less than for TCAs.

Special points Escitalopram is the active enantiomer of citalopram. Sertraline and escitalopram are the SSRIs which are most selective for 5-HT uptake inhibition.

R&D 7e Ch 46, pp 573-574; D&H 2e Ch 40, pp 92-93

Stylised cardiac action potential. Antidysrhythmic drugs can affect different phases of the action potential.



A class II antidysrhythmic (Similar drugs: esmolol, atenolol.)

Propranolol

Actions Antidysrhythmic. (Also antihypertensive, antianginal.) Blocks actions of catecholamines on β-adrenoceptors (see card 2.02).

MOA Blocks sympathetic drive, reducing pacemaker activity (phase 4) and increasing AV conduction time. Reduces the slow inward Ca^{2+} current which affects phase 2 of the action potential. Propranolol has additional class I action. Esmolol and atenolol are β_1 selective.

Abs/Distrib/Elim Oral admin. $T_{0.5}$ s: propranolol – 4h, atenolol – 6h, esmolol – 10min.

Clinical use Reduction of mortality after infarct (where dysrhythmias have a sympathetic input). Paroxysmal atrial fibrillation. Esmolol's short $T_{0.5}$ allows its use by i.v. infusion for emergency treatment of supraventricular dysrhythmias.

Adverse effects Bronchoconstriction in asthmatic patients. Cardiac slowing with possible heart block. Propranolol has CNS effects: depression, sedation and sleep disturbances.

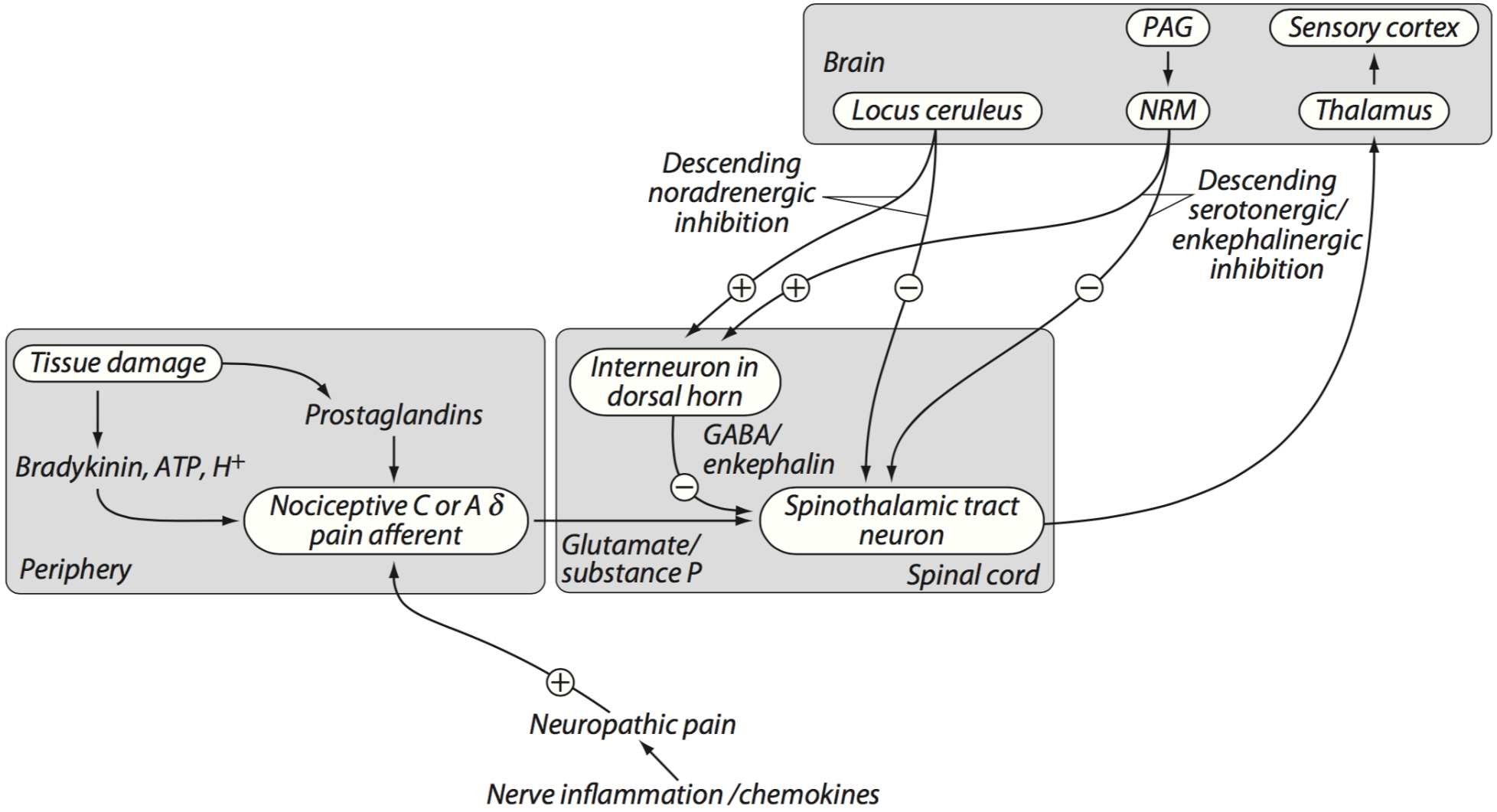
R&D 7e Ch 21, p 257; D&H 2e Ch 18, pp 46-47

Lecture #5 | Drugs used in management of pain

26.01 Morphine

Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Opioid receptor agonist (Similar drugs: diamorphine (heroin), buprenorphine, codeine)

Morphine

Actions Analgesia. Sedation. Euphoria/reduced anxiety. Physical/psychological dependence. Cough suppression and respiratory depression. Inhibition of gut motility.

MOA Activates μ opioid receptors in the brain and spinal cord to inhibit pain transmission and modify the central perception of pain. Activation of κ receptors may exert an additional effect on pain transmission in the spinal cord. May inhibit the activation of sensory nerve endings. Opioid receptors are G-protein coupled receptors which inhibit adenylate cyclase activity, open K^+ channels and inhibit the opening of Ca^{2+} channels in nerve endings.

Abs/Distrb/Elim Oral or s.c., i.m. injection. Glucuronic acid conjugation in liver: $t_{0.5}$ 3–4h. The actions of diamorphine and codeine are due, at least in part, to metabolism to morphine. Buprenorphine $T_{0.5}$ 12h.

Clinical use Moderate to severe chronic and post-operative pain (codeine – mild pain). Epidural anaesthesia. Neuropathic pain. Treatment of painful cough. Diarrhoea.

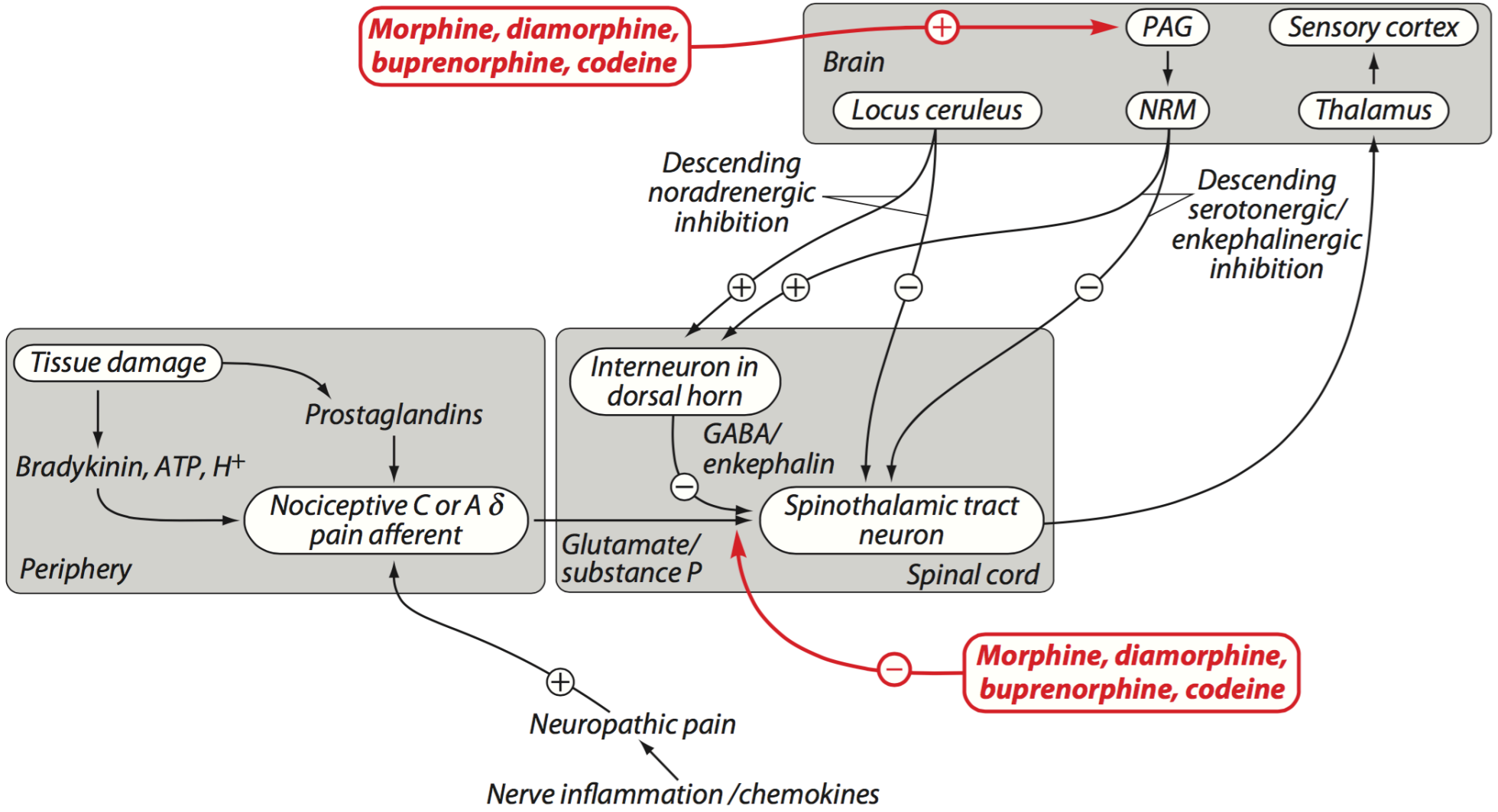
Adverse effects Hypotension. Constipation, nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects (much less with codeine). Larger doses – coma with respiratory depression.

R&D 7e Ch 41, pp 510-513; D&H 2e Ch 42, p 96

26.02 Pethidine (Meperidine)

Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Opioid receptor agonist (Similar drugs: fentanyl, remifentanil, sufentanil)

Pethidine

Actions Analgesia. Euphoria. Physical/psychological dependence. Respiratory depression. Inhibition of gut motility. (Antimuscarinic effects of pethidine cause tachycardia.)

MOA Activates μ opioid receptors in the brain and spinal cord to inhibit pain transmission. Activation of κ receptors may exert an additional effect on pain transmission in the spinal cord. May inhibit activation of the sensory nerve endings. (See also 'Morphine' – card 26.01).

Abs/Distrb/Elim Oral/ i.m. admin. Subject to hydrolysis and P450 oxidation – $T_{0.5}$ 3–5h. Fentanyl is also available as a patch for transdermal admin. for long-term effects. Remifentanil has a very short half-life (0.1h).

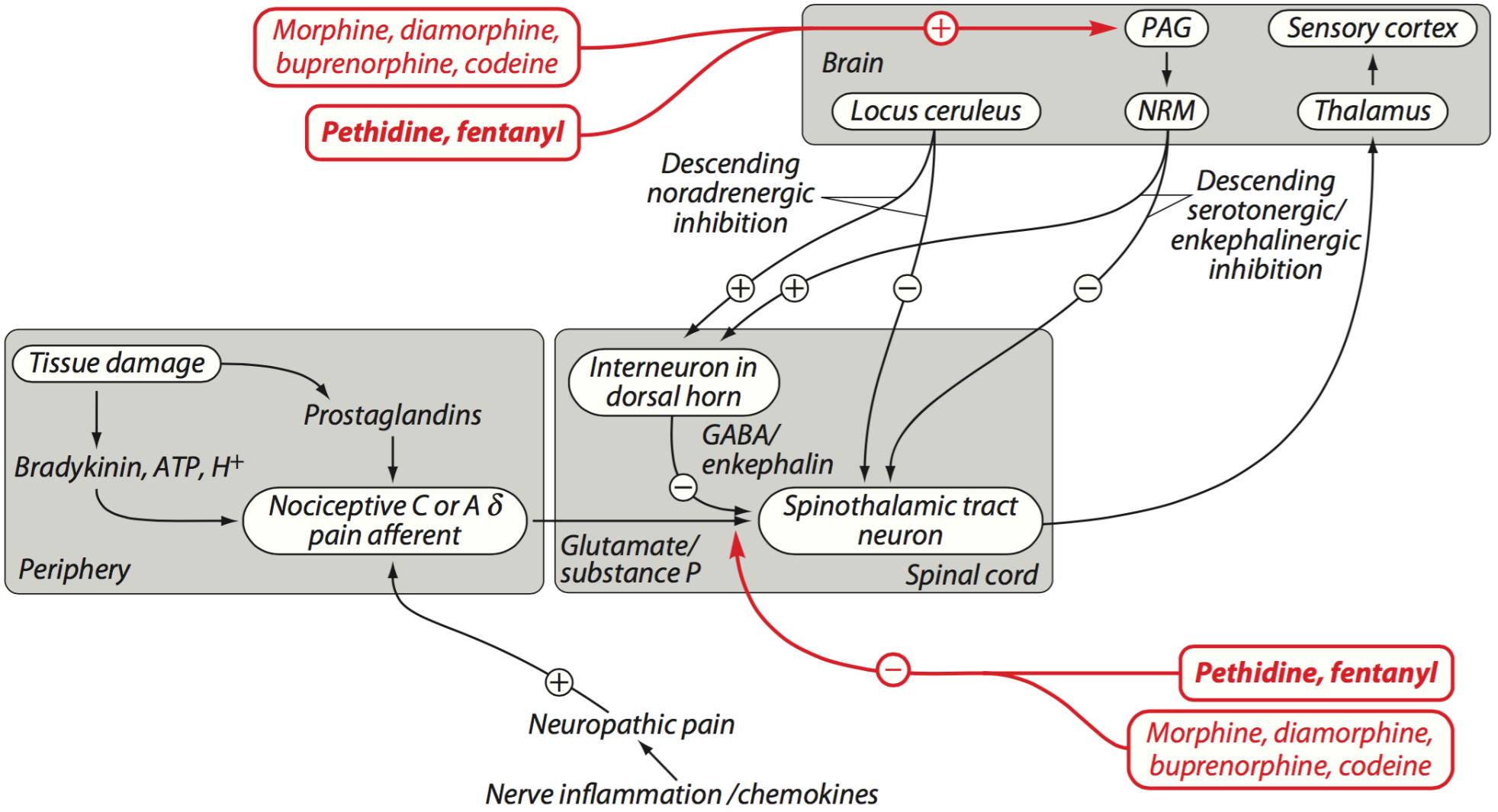
Clinical use Moderate to severe pain. Does not reduce uterine contractions so favoured for labour pain. Remifentanil and sufentanil are given i.v. for surgical analgesia.

Adverse effects Constipation (less than morphine), nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects. Larger doses – coma with respiratory depression.

R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

26.03 **Methadone** Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Opioid receptor agonist (Similar drug: propoxyphene (active d-isomer-dextropropoxyphene))

Methadone

Actions Analgesia (methadone strong, propoxyphene weak). Euphoria. Physical/psychological dependence. Respiratory depression. Inhibition of gut motility.

MOA Activation of μ opioid receptors in the brain and spinal cord to inhibit pain transmission. Also modifies the central perception of pain. Opioids may also inhibit the activation of sensory nerve endings. (See also 'Morphine' – card 26.01.)

Abs/Distrb/Elim Oral absorption. Long duration of action. P450 metabolism in liver $T_{0.5}$ 15–40h. Propoxyphene $T_{0.5}$ 6h.

Clinical use Analgesia (propoxyphene only copes with mild to moderate pain). Maintenance of opioid addicts and assistance in withdrawal program. Cough suppression. Propoxyphene is often combined with paracetamol.

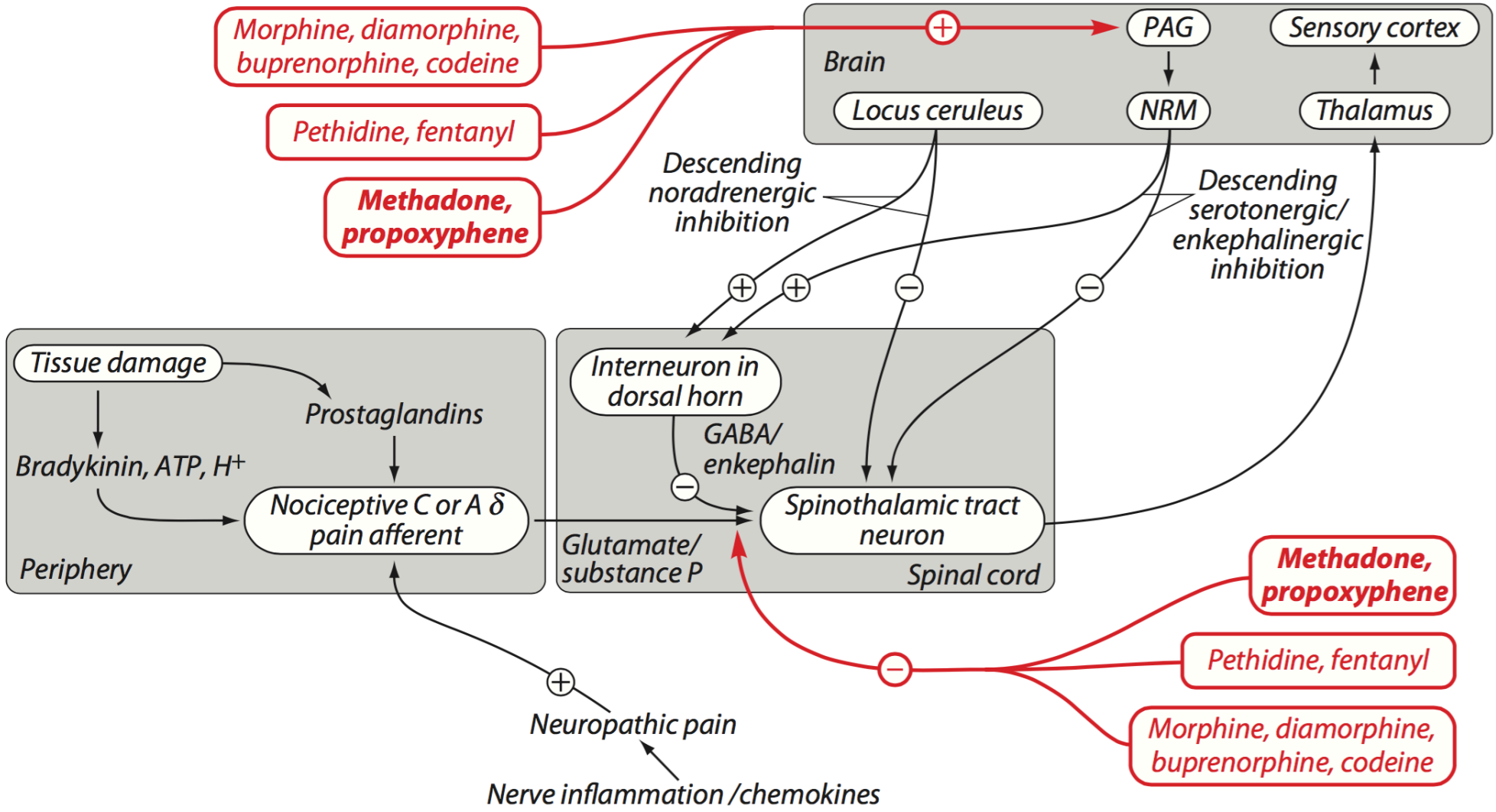
Adverse effects Constipation, nausea, vomiting, drowsiness, dizziness. Tolerance, dependence and withdrawal effects. Larger doses – coma with respiratory depression and possible cardiac dysrhythmia.

R&D 7e Ch 41, pp 519-520; D&H 2e Ch 42, p 96

26.04 Tramadol

Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Atypical narcotic analgesic

Tramadol

Actions Analgesia.

MOA Weak agonist action at μ opioid receptors but main action is attributed to enhancement of monoamine neurotransmission by inhibition of 5-HT and noradrenaline reuptake into nerve endings. Analgesic action is reported to be inhibited by 5-HT_3 receptor antagonists.

Abs/Distrb/Elim Oral admin. Subject to hepatic demethylation and conjugation, $T_{0.5}$ 6h.

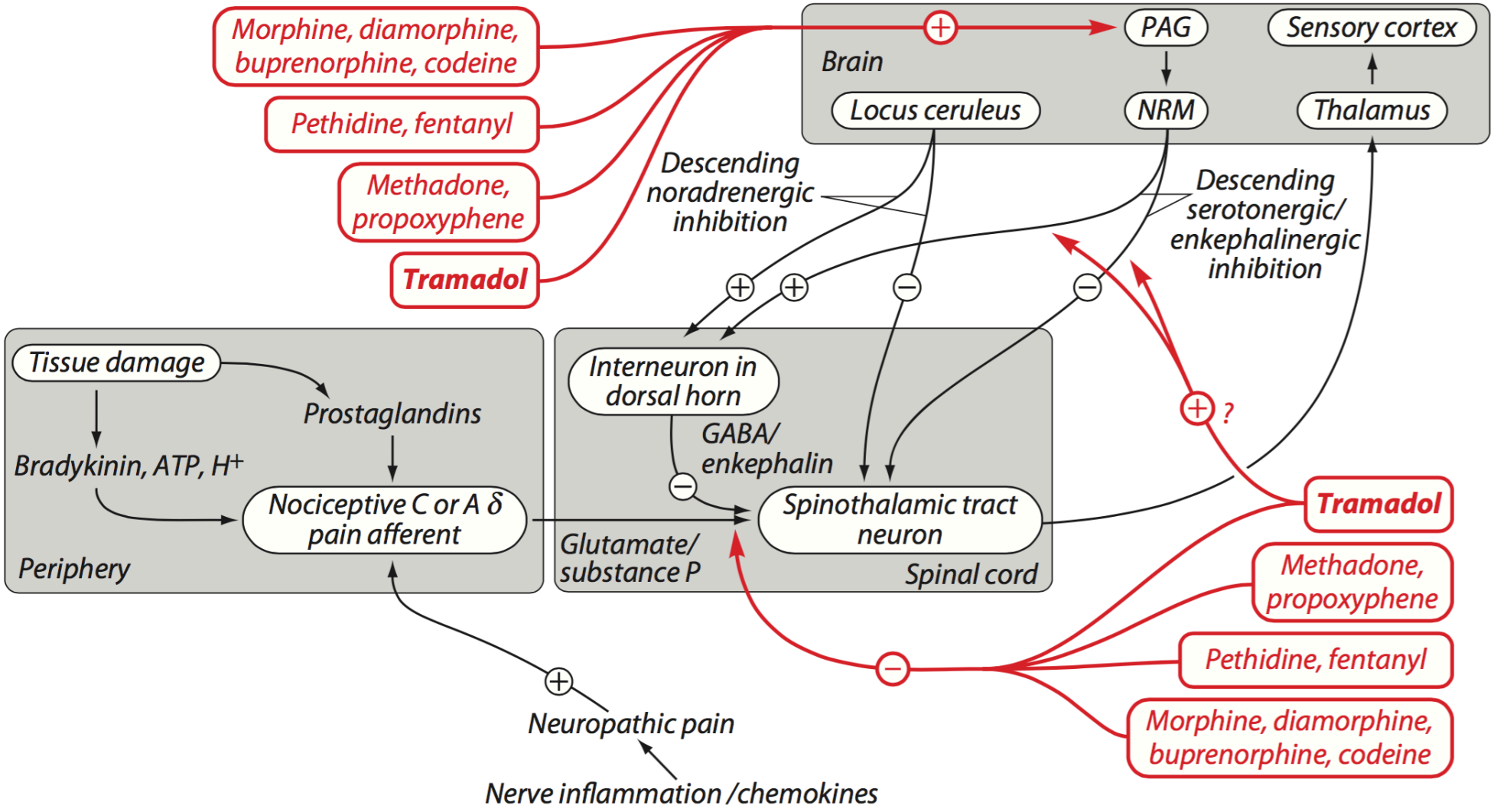
Clinical use Moderate/moderately severe pain. Used post-operatively. Neuropathic pain.

Adverse effects Dizziness, nausea and vomiting. Respiratory depression, constipation and addiction (but less than with morphine). Convulsions.

R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

26.05 **Naloxone** Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Opioid receptor antagonist (Similar drug: naltrexone)

Naloxone

Actions Antagonises the actions of opioid drugs. May cause hyperalgesia under conditions, such as stress, where endogenous opioids may be operative.

MOA Competitive antagonist of opioids at μ, δ and κ-receptors.

Abs/Distrb/Elim Given by injection (i.v., i.m. or s.c.) (very low oral bioavailability). Conjugated with glucuronic acid in liver, short $t_{1/2}$:1–2h. Naltrexone is orally active and has a $t_{1/2}$ of 4h though action is extended by an active metabolite with $t_{1/2}$ of 13h.

Clinical use Treatment of respiratory depression and coma caused by opioid overdose. The longer-acting naltrexone is used to aid in treating opioid and alcohol addiction.

Adverse effects Free of important side effects. May cause withdrawal symptoms in opiate addicts.

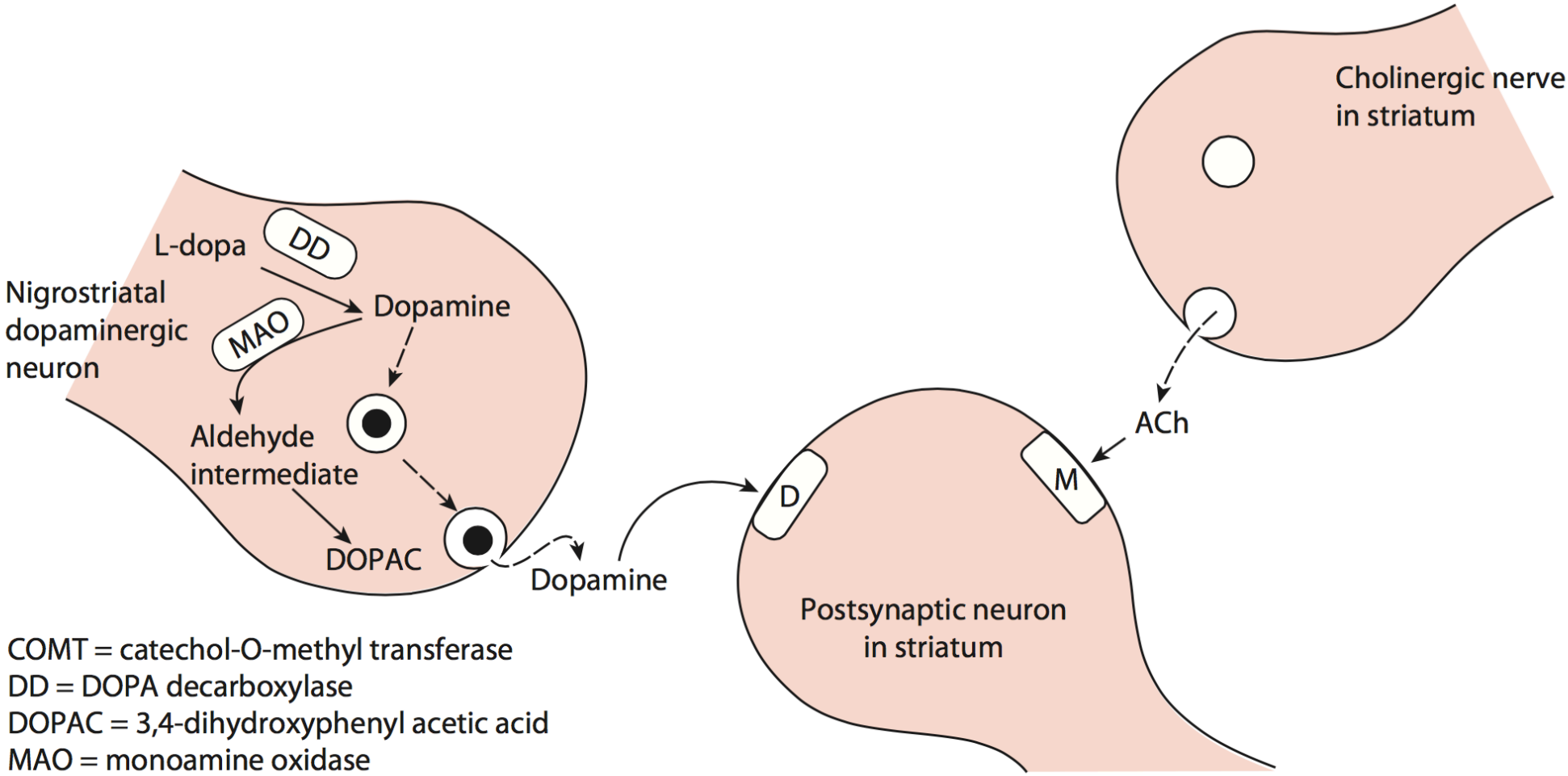
R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

Lecture #6 | Drugs used in Parkinsonism

20.01 Levodopa (L-dopa) – carbidopa

Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Levodopa – precursor of dopamine
Carbidopa – peripheral DOPA decarboxylase inhibitor (Similar drug: benserazide)

Levodopa/ Carbidopa

Actions Antiparkinsonian.

MOA Decarboxylation of levodopa to dopamine restores some activity in nigrostriatal pathway. Carbidopa inhibits levodopa decarboxylation outside the brain, allowing the use of smaller doses and reducing peripheral side effects of dopamine (e.g. postural hypotension).

Abs/Distrib/Elim Oral admin. Levodopa $T_{0.5}$ 1–2h when co-administered with carbidopa.

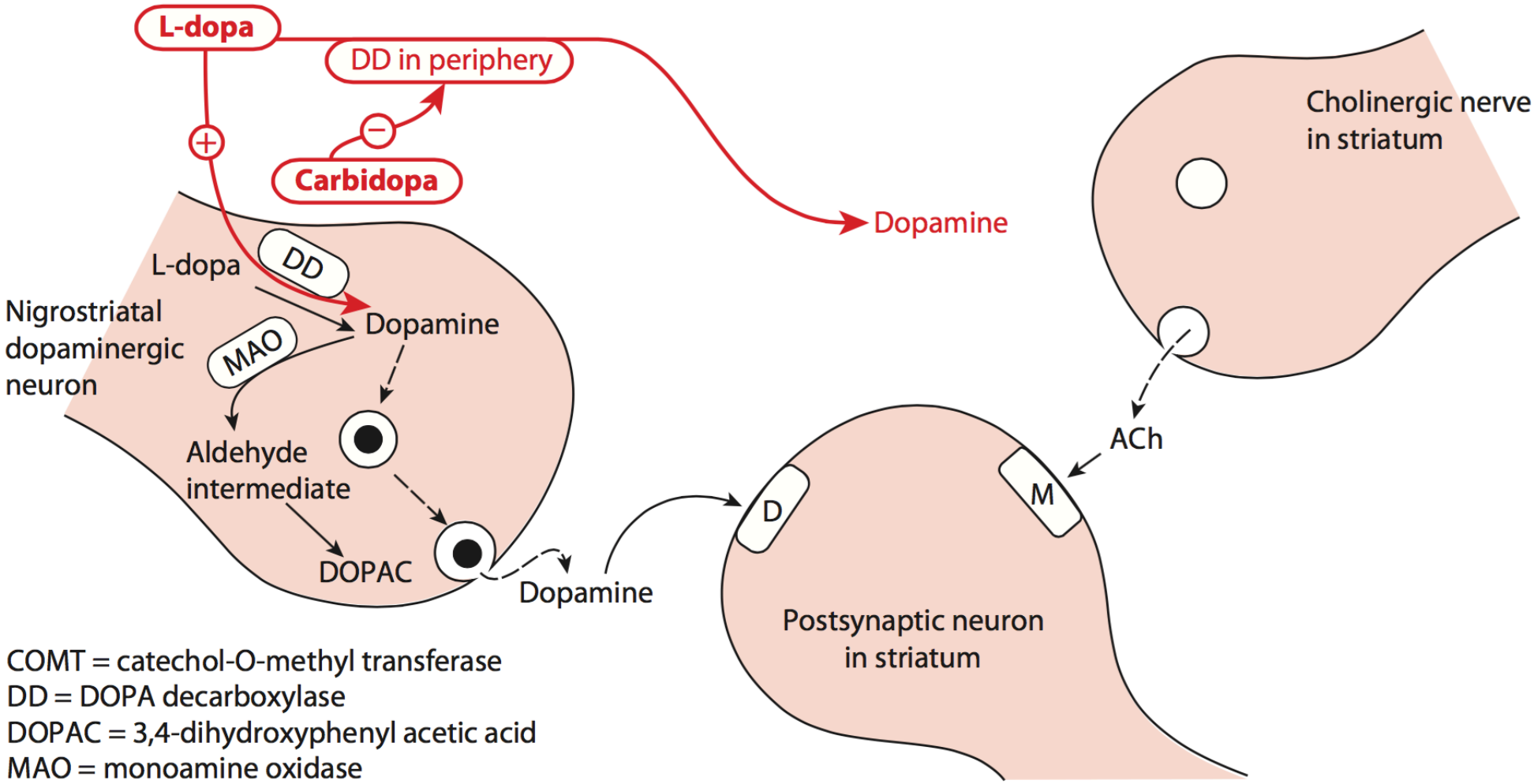
Clinical use Cornerstone of therapy in Parkinson's disease. Levodopa is usually given with a peripheral DOPA decarboxylase inhibitor. More effective against akinesia and rigidity than against tremor. Effectiveness diminishes over some months to a few years.

Adverse effects Anorexia, nausea and vomiting. Postural hypotension. Acute schizophrenia-like syndrome. Confusion, anxiety, disorientation and insomnia or nightmares. More slowly developing effects: dyskinesia (in most patients after 2 years) and 'on-off' effects (rapid fluctuations between dyskinesia and hypokinesia/rigidity).

R&D 7e Ch 39, pp 487-488; D&H 2e Ch 36, p 85

20.02 **Entacapone** Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Catechol-O-methyl transferase inhibitor

Entacapone

Actions Synergises with the antiparkinsonian effects of levodopa/carbidopa. Potentiates actions of catecholamines.

MOA Reversible inhibition of COMT in the periphery reduces levodopa breakdown (like peripheral dopa decarboxylase inhibitors) allowing more of levodopa dose to penetrate brain.

Abs/Distrib/Elim Oral admin. Short $T_{0.5}$ (1h) necessitates dosing several times/day.

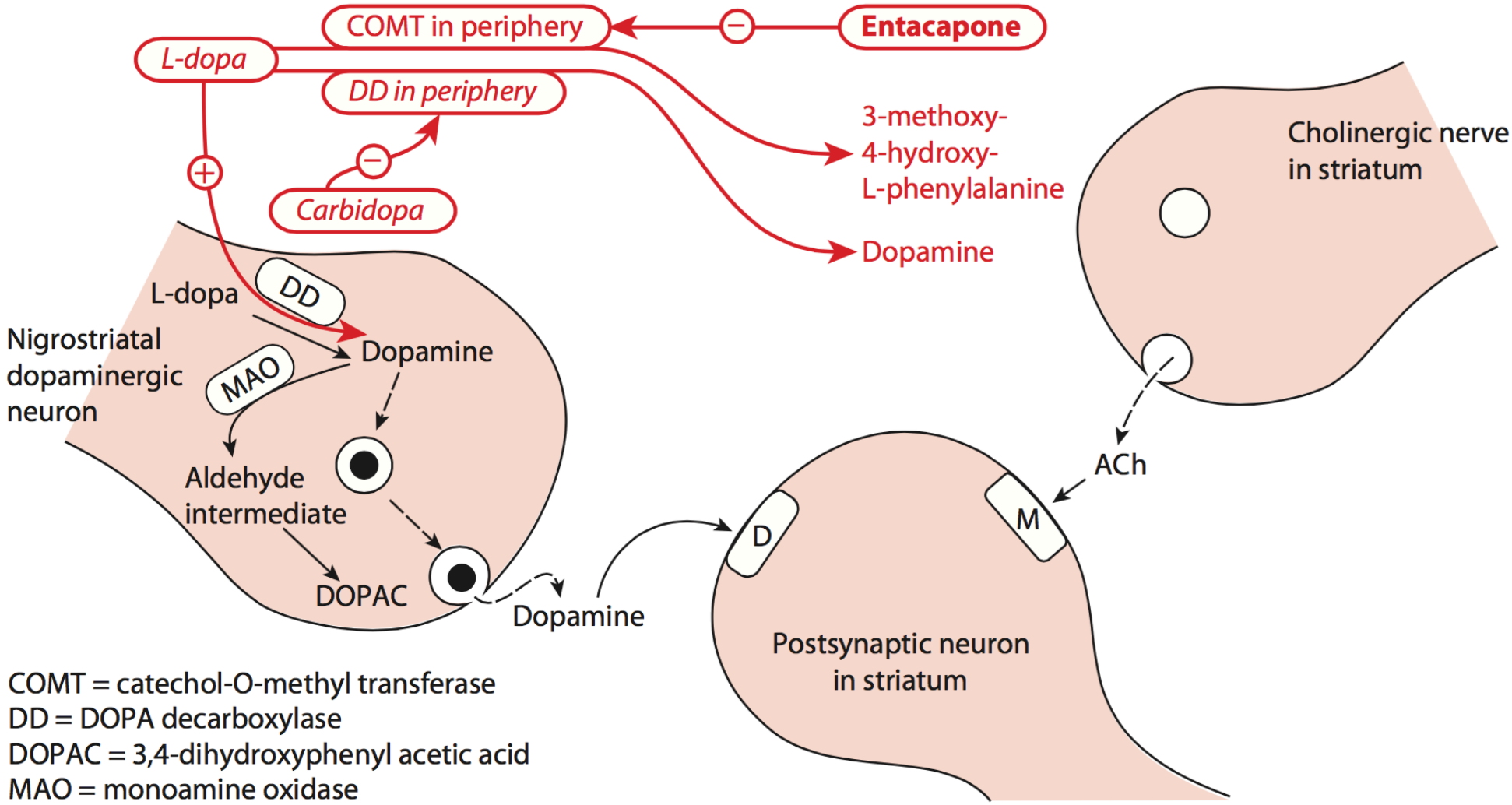
Clinical use Adjunct to levodopa/carbidopa therapy – especially for patients showing 'end of dose' symptoms. (No antiparkinsonian effect by itself.)

Adverse effects Exacerbates adverse effects of levodopa/carbidopa taken at the same time. Dyskinesia, nausea, diarrhoea. Postural hypotension. Hallucinations. Anxiety and sleepiness.

R&D 7e Ch 39, p 487; D&H 2e Ch 36, p 85

20.03 **Selegiline** Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

MAO_B inhibitor (Similar drug; rasagiline)

Selegiline

Actions Antiparkinsonian.

MOA Selective irreversible inhibition of MAO_B, the isozyme which has dopamine as a preferred substrate. Potentiates action of endogenous dopamine and dopamine formed from administered levodopa.

Abs/Distrib/Elim Oral admin. (but low bioavailability), $t_{½}$ 2h. Rasagiline $T_{0.5}$ 3h.

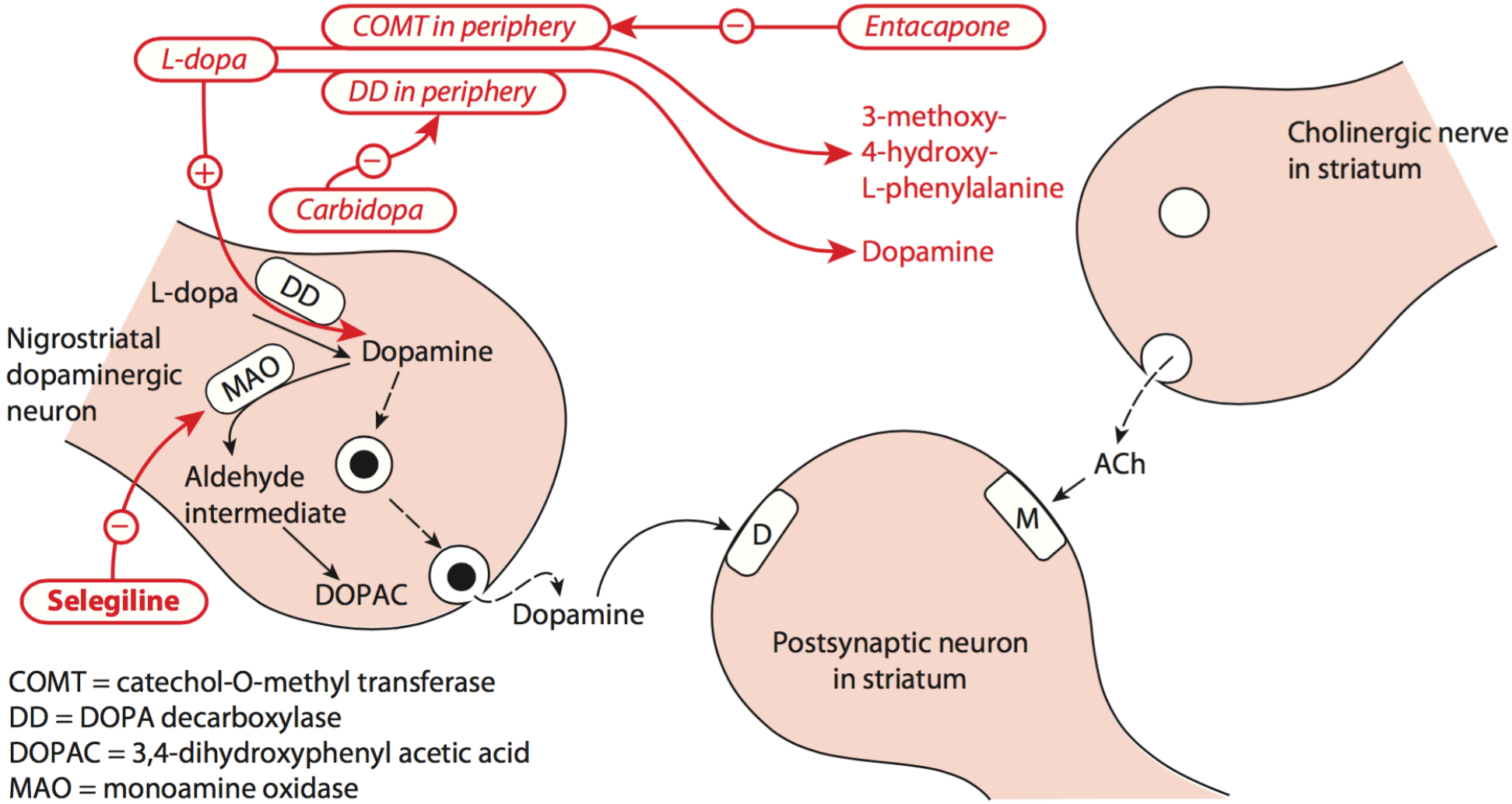
Clinical use Adjunct to levodopa/carbidopa, as their effect wanes, in Parkinson's disease. Irreversible nature of MAO inhibition prolongs effects of drug for some days. Also approved for major depression.

Adverse effects Adverse effects mainly due to increased action of levodopa taken concurrently: nausea, dyskinesia depression, insomnia, postural hypotension, hallucinations, confusion. At clinical doses, spares MAO_A so less likely to provoke the 'cheese reaction' than non-selective MAO inhibitors. Severe interactions may occur with tricyclic and SSRI antidepressants.

R&D 7e Ch 39, p 488; D&H 2e Ch 36, p 85

20.04 **Bromocriptine** Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Dopamine receptor agonist (Similar drugs: pramipexole, ropinirole)

Bromocriptine

Actions Antiparkinsonian. Inhibits prolactin secretion from pituitary.

MOA Activation of D_2 receptors on striatal neurones counters impairment of dopaminergic transmission. Actions on D_1 receptors may be important in ameliorating the non-Parkinsonian symptoms associated with disease.

Abs/Distrib/Elim Dopamine agonists have longer $T_{0.5}$s than levodopa and provide a more continuous control of symptoms. $T_{0.5}$: bromocriptine 12h, pramipexole 12h, ropinirole 6h.

Clinical use Used alone or as adjuvants to levodopa therapy in Parkinson's. Often used in early stages before use of levodopa. Bromocriptine's effect on prolactin secretion is used for amenorrhoea and acromegaly.

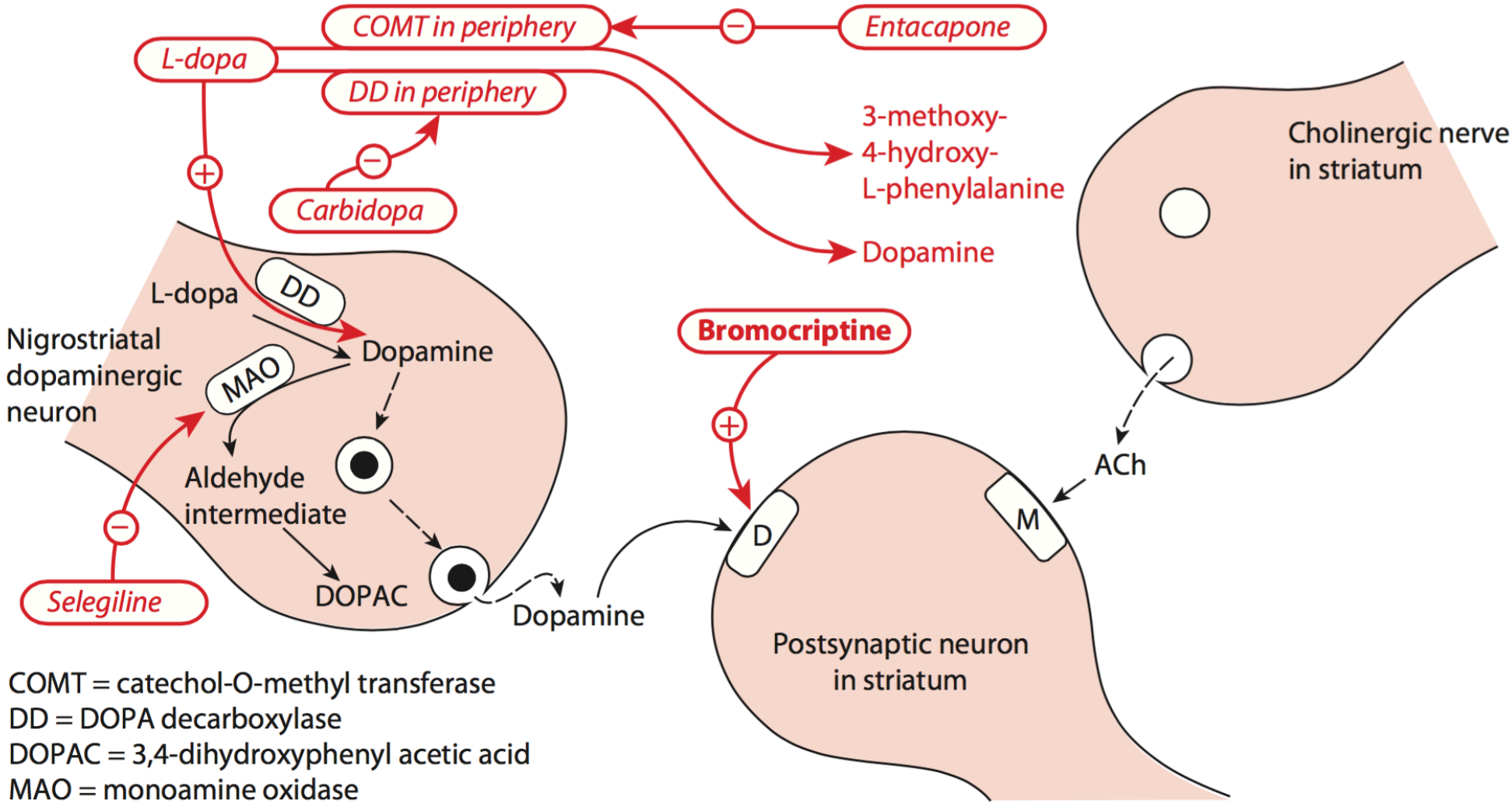
Adverse effects Hallucinations and sleepiness (more than with levodopa). Postural hypotension. Dyskinesias – but less than with levodopa. Bromocriptine (and other ergot derivatives) rarely cause fibrotic reactions.

R&D 7e Ch 39, p 488; D&H 2e Ch 36, p 85

20.05 Amantadine

Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Antiviral agent with unrelated use in Parkinson's disease

Amantadine

Actions Antiparkinsonian. Antiviral.

MOA Thought to act by increasing dopamine release from nerve endings in striatum. Antimuscarinic actions, like those of benztropine, may also contribute.

Abs/Distrib/Elim Oral admin. Most excreted unchanged in urine. $T_{0.5}$ 17h.

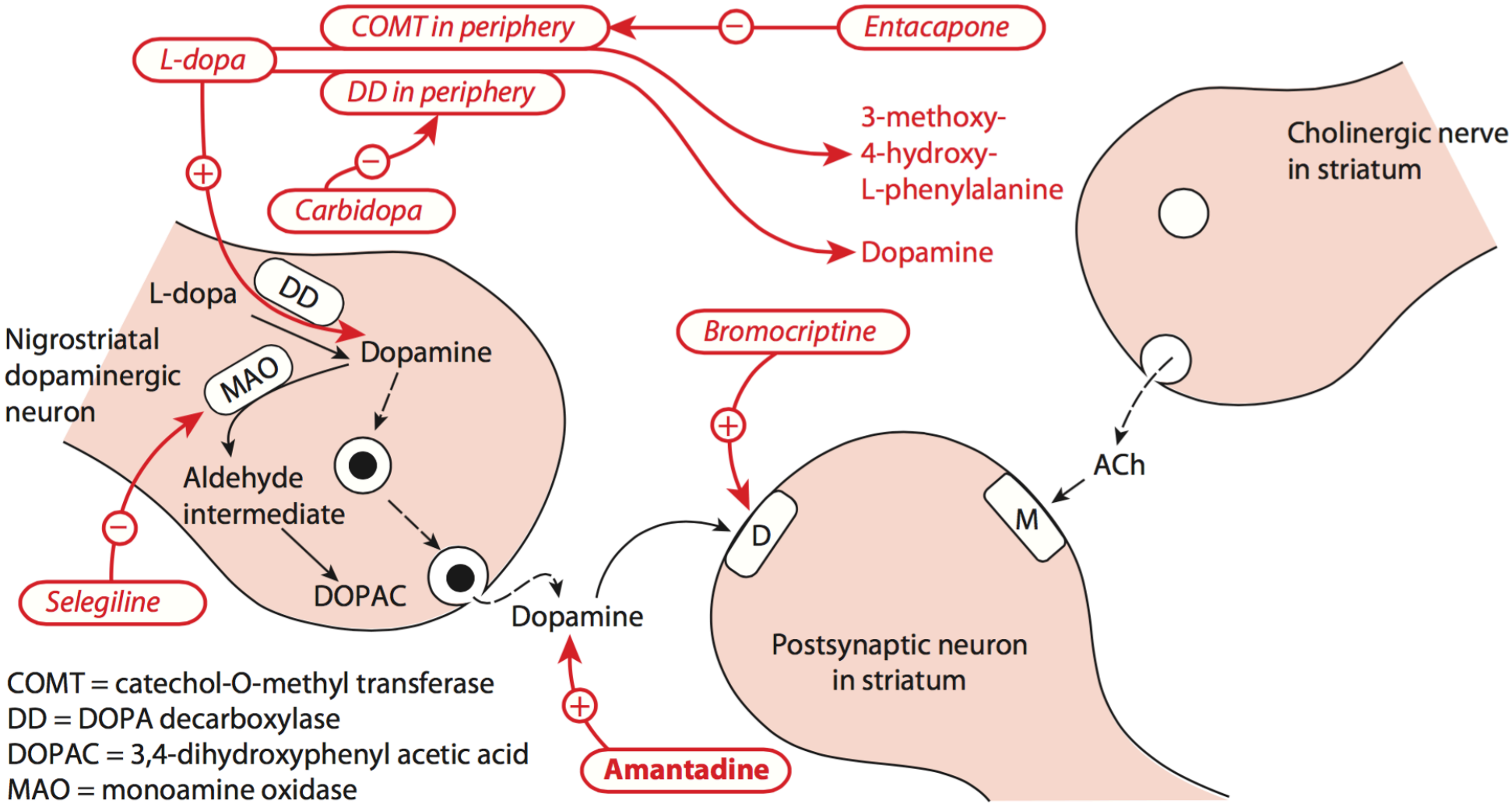
Clinical use Parkinson's disease. Generally less effective than levodopa, dopamine agonists or MAO_B inhibitors. Also effective against the dyskinesia associated with levodopa therapy. (Antiviral action used for influenza infection.)

Adverse effects Nausea, dizziness, insomnia. Postural hypotension. Anxiety, confusion, hallucinations. Antimuscarinic action is important contributor to death from overdose .

R&D 7e Ch 39, p 489; D&H 2e Ch 36, p 85

20.06 **Benztropine** Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Centrally acting muscarinic antagonist (Similar drugs: trihexyphenidyl, biperiden)

Benztropine

Actions Antiparkinsonian.

MOA Reduces muscarinic actions of ACh in striatum. (Restores 'balance' between dopaminergic and cholinergic activities.) Action is probably on M_1 receptors

Abs/Distrib/Elim Orally active. Long $T_{0.5}$ – 36h. Trihexyphenidyl $T_{0.5}$ 3–4h.

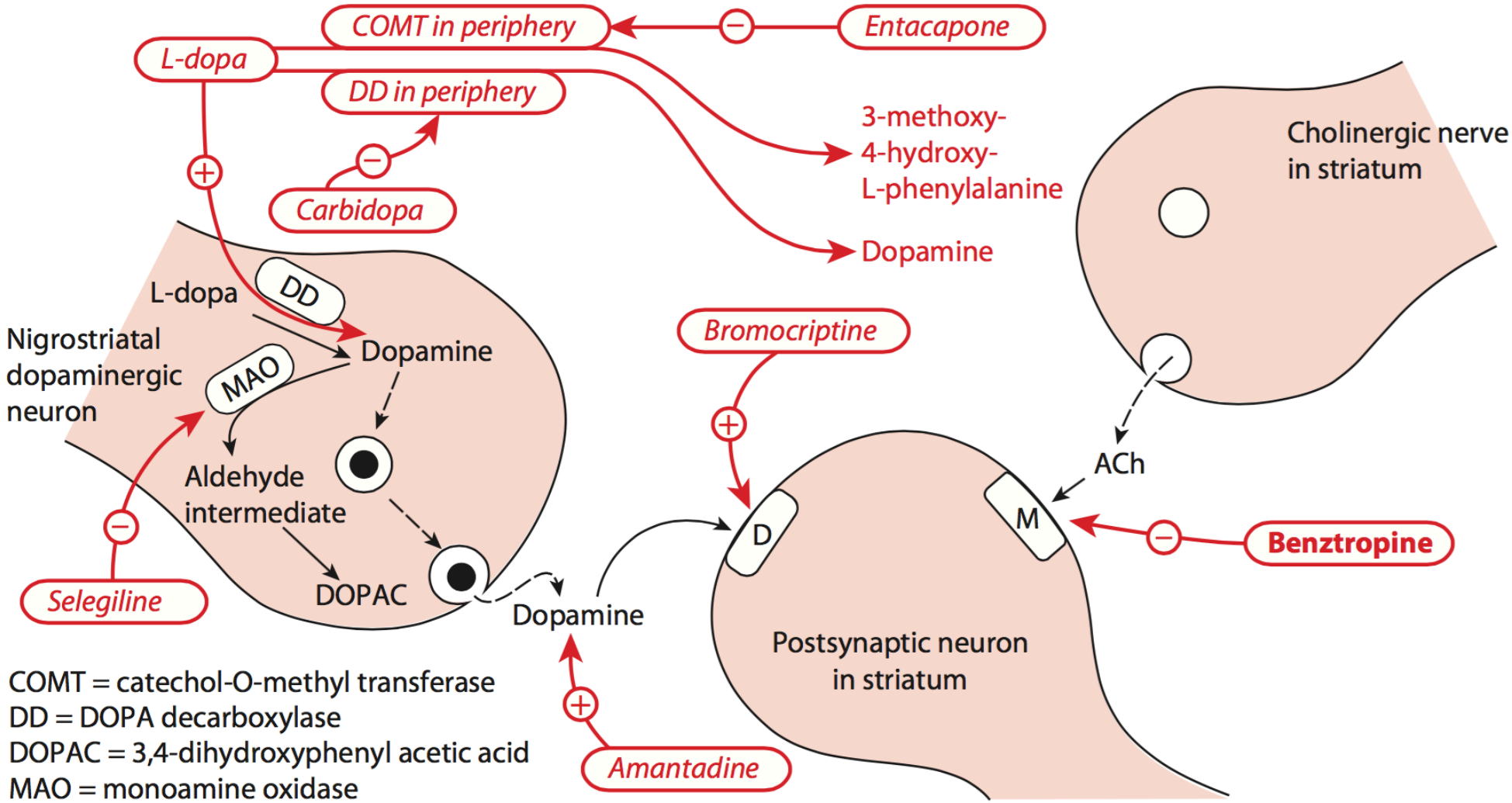
Clinical use Second-line drug for Parkinson's disease. Much less effective than those drugs increasing dopaminergic transmission but has value in treating tremor. Used as adjunct with other agents and in drug (antipsychotic)-induced Parkinsonism.

Adverse effects Effects due to parasympathetic block – dry mouth, inhibition of peristalsis, raised intraocular pressure (avoid in narrow-angle glaucoma), blurred vision, urinary retention, tachycardia, etc. Confusion, hallucinations.

R&D 7e Ch 39, p 489; D&H 2e Ch 36, p 85

20.07 **Summary** Neurodegenerative disorders: Parkinson's

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



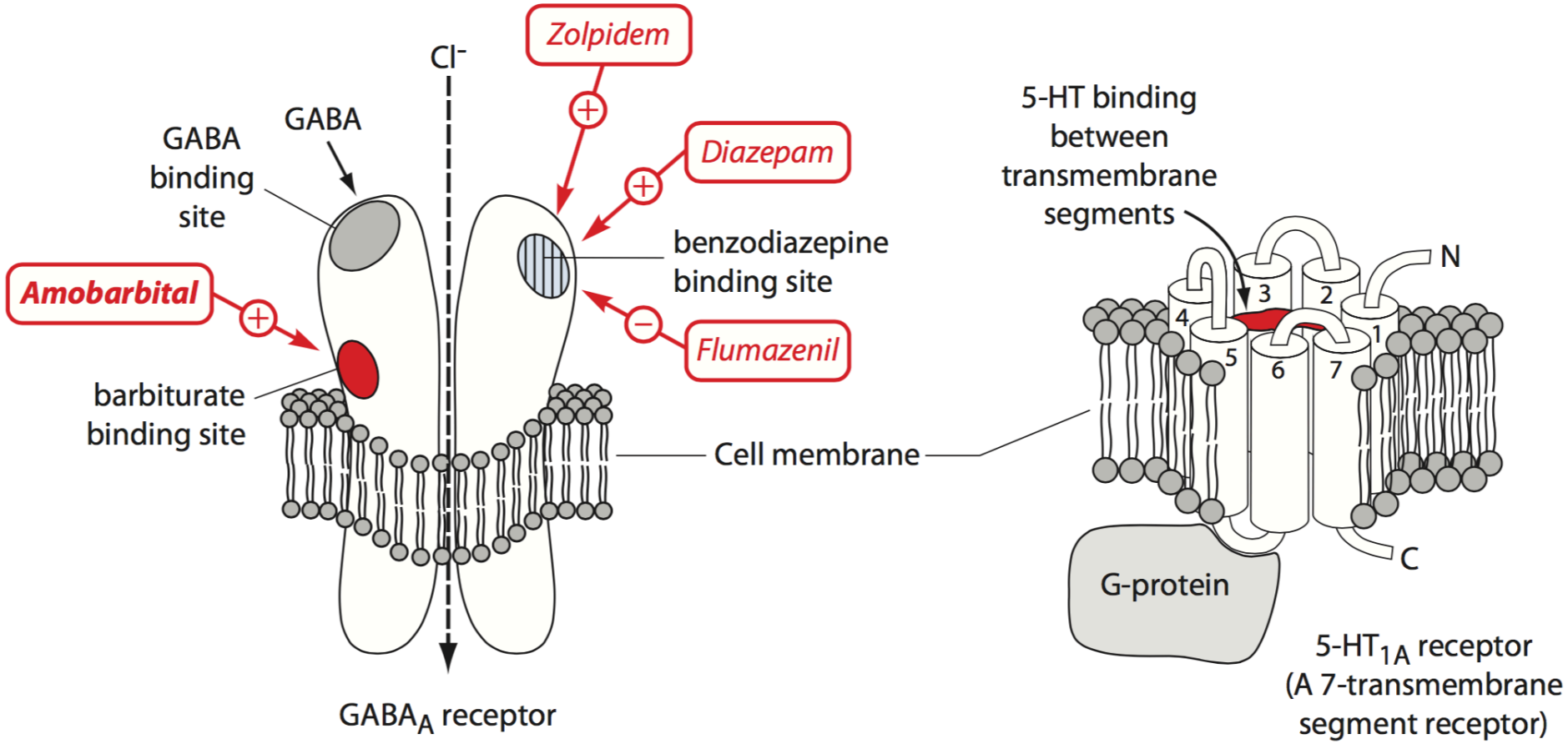
COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

Lecture #7 | Drugs used in anxiety and panic disorders

22.05 Buspirone

Anxiolytics and hypnotics

The important anxiolytic and hypnotic drugs act on $GABA_A$ or $5HT_{1A}$ receptors.



Non-sedating anxiolytic

Buspirone

Actions Anxiolytic.

MOA Partial agonist at 5-HT_{1A} receptors. Acts presynaptically to inhibit firing of serotonergic neurons, particularly in the dorsal raphe nucleus. (Actions on postsynaptic 5-HT_{1A} receptors in amygdala also likely.) Clinical response is not seen for 1–2 weeks, suggesting effects may require more complex, plastic changes.

Abs/Distrb/Elim Given orally, but significant first-pass metabolism. $T_{0.5}$ 2–3h, but effects are longer lasting, possibly due to metabolite with similar action.

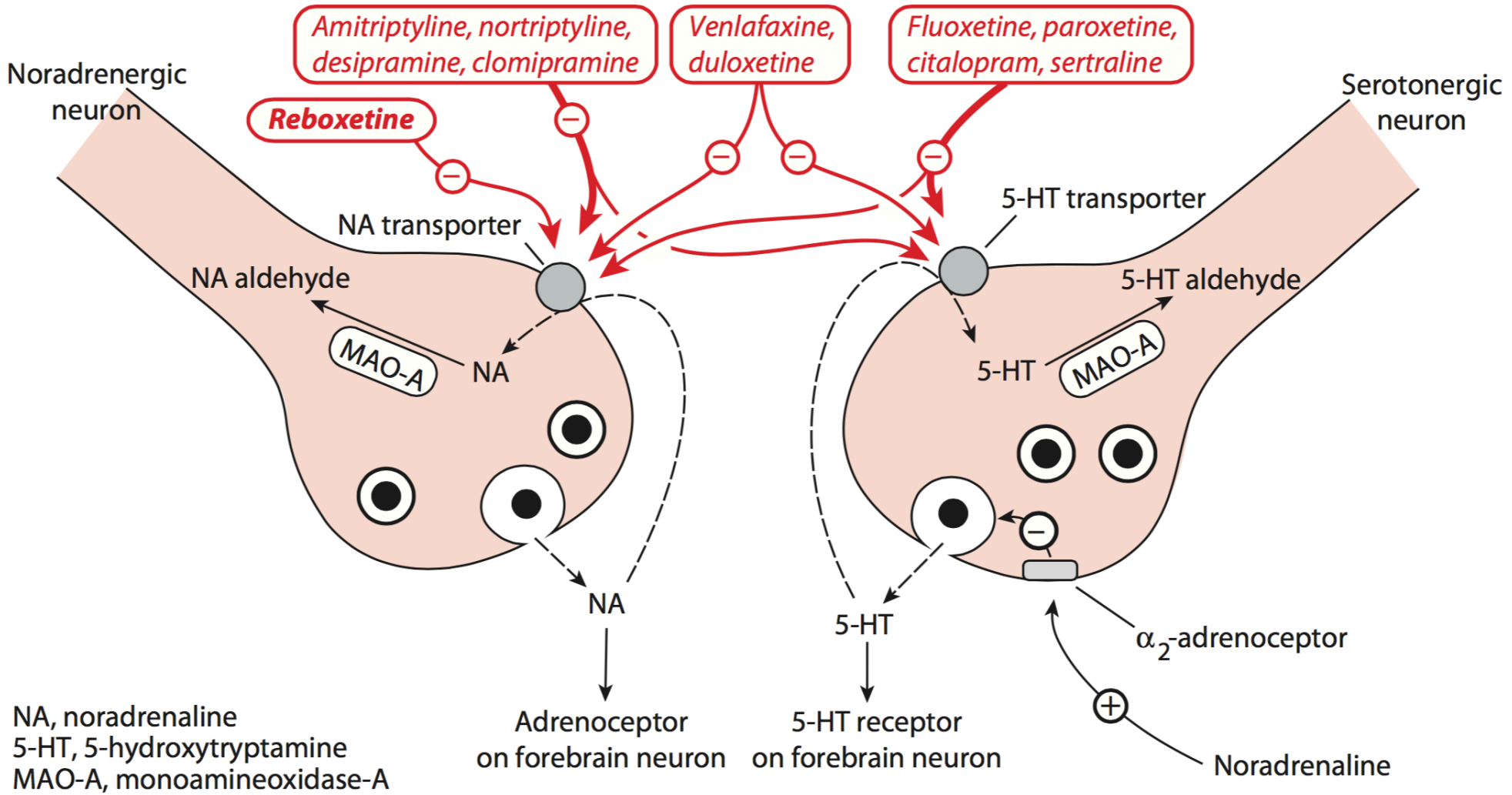
Clinical use Generalised anxiety disorder.

Adverse effects Nausea, dizziness, nervousness, headache. Blurred vision. (Does not cause dependence, nor cause the sedation and motor incoordination seen with benzodiazepines.)

R&D 7e Ch 43, pp 438-439; D&H 2e Ch 38, p 88

24.05 **Phenelzine** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



Monoamine oxidase inhibitor (MAOI) (Similar drugs: isocarboxazid, moclobemide)

Phenelzine

Actions Antidepressant.

MOA Phenelzine and isocarboxacid irreversibly inhibit both the A & B forms of monoamine oxidase. MAO is found in nerve endings, MAO-A acting preferentially on noradrenaline and 5-HT and MAO-B acting mainly on dopamine. MAO inhibition increases the amount of transmitter in the nerve-ending. Antidepressant action is due to MAO-A inhibition. Moclobemide is a selective, reversible inhibitor of MAO-A. (MAO-B inhibitors are used for Parkinson's disease (see card 20.03).)

Abs/Distrib/Elim Oral administration. Plasma half-life 1–2h, but action lasts much longer because of irreversible inhibition of MAO. Moclobemide $T_{0.5}$ 1–2h.

Clinical use Depression; may have particular value for atypical depression. Social phobia. Clinical effect takes some days to develop.

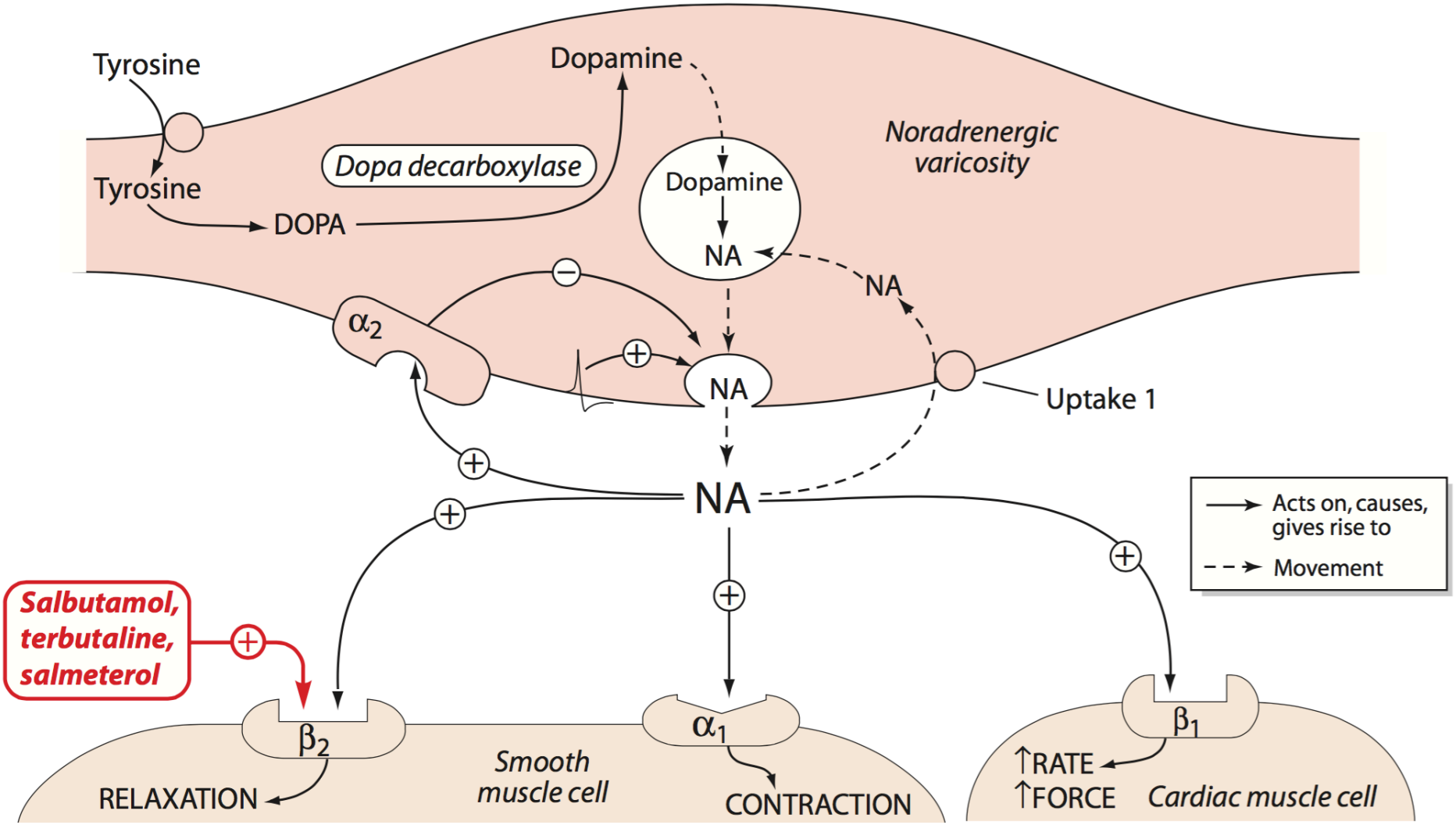
Adverse effects Postural hypotension. Headache. Insomnia. Sexual dysfunction. Dry mouth, urinary retention. Convulsions with overdose. Increased risk of suicide in young patients. Cheese reaction with dietary tyramine – hypertensive crisis. Cheese reaction is less pronounced with moclobemide (since MAO-B is still functional).

Special points Adverse effects are more frequent than with the TCAs or SSRIs so MAOIs are second-line treatment for depression.

R&D 7e Ch 46, pp 577-578; D&H 2e Ch 40, pp 92-93

2.02 Atenolol — Noradrenergic transmission

The figure gives a simple outline of noradrenergic transmission



A β1 antagonist (Similar drugs: metoprolol, oxprenolol, propranolol; some selective, some not)

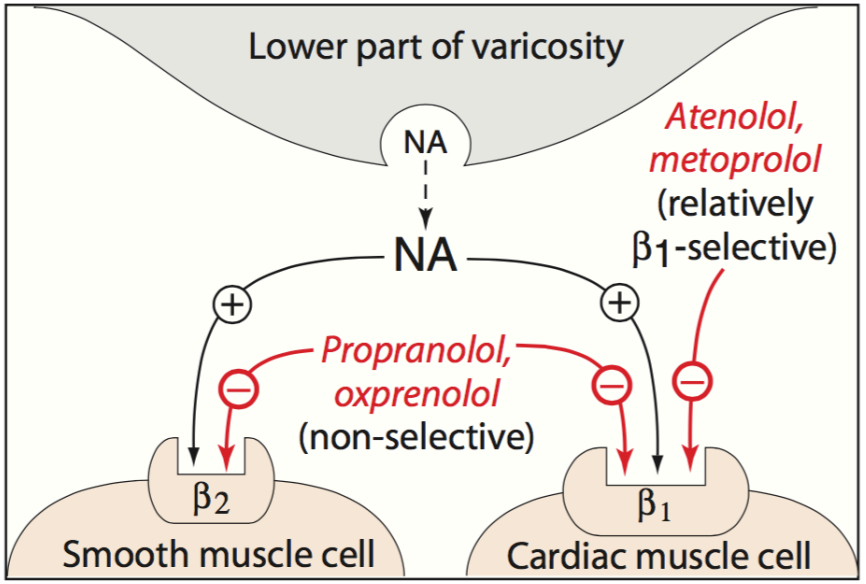
Atenolol

Actions Reduces BP in hypertensive patients by
↓causing: cardiac output
↓renin release
↓CNS-mediated sympathetic activity
In angina slows heart and reduces metabolic demand.

MOA Block of the action of endogenous and exogenous agonists on β_1-receptors.

Abs/Distrb/Elim Absorbed orally; plasma $t_{½}$ 4h; metabolised by liver.

Clinical use Hypertension. Angina. Prevention of dysrhythmia in myocardial infarction.



Adverse effects Dangerous: bronchconstriction in asthma, in emphysema; potential heart block or heart failure in patients with coronary disease ; decreased sympathetic warning to hypoglycemia in diabetic patients. Inconvenient: cold extremities, fatigue.

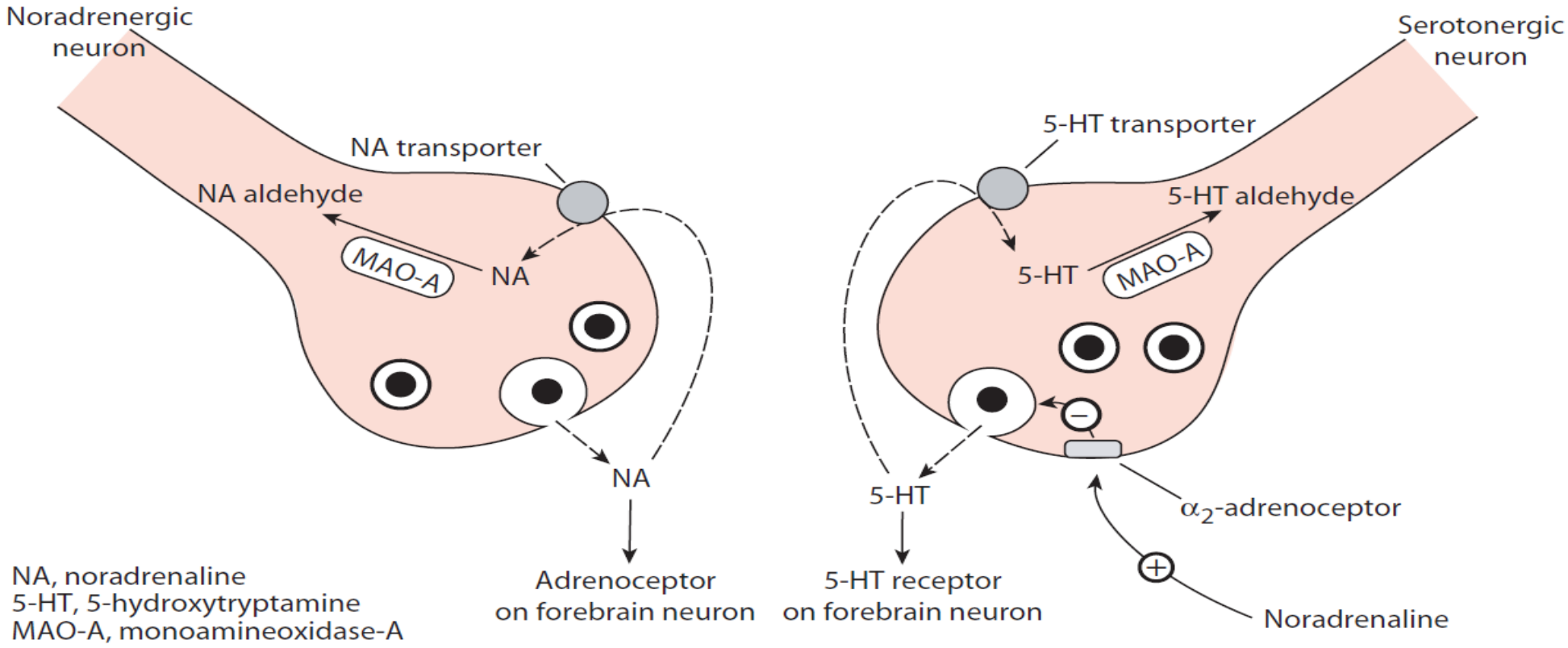
Special points Atenolol is water-soluble, can enter the CNS and may cause nightmares. Oxprenolol has some intrinsic sympathomimetic activity and thus causes less bradycardia and less coldness of hands and feet.

R&D 7e Ch 14, p 187-188; D&H 2e Ch 11, pp 32-35

Lecture #8,10 | Drugs used in depression Old & New

24.01 **Amitriptyline** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Tricyclic antidepressant (TCA) (Similar drugs: nortriptyline, desipramine, clomipramine)

Amitriptyline

Actions Antidepressant.

MOA Inhibits reuptake of noradrenaline into noradrenergic neurons and 5-HT into serotonergic neurons, so potentiating transmitter action. The clinical effects are not seen for a few weeks, meaning that longer-term changes (e.g. down-regulation of receptors) are required.

Abs/Distrib/Elim Oral administration. Metabolised in liver by cytochrome P450 system with subsequent conjugation reactions. Plasma half-life 12–24h (influenced by P450 inhibitors or inducers). Strong protein binding.

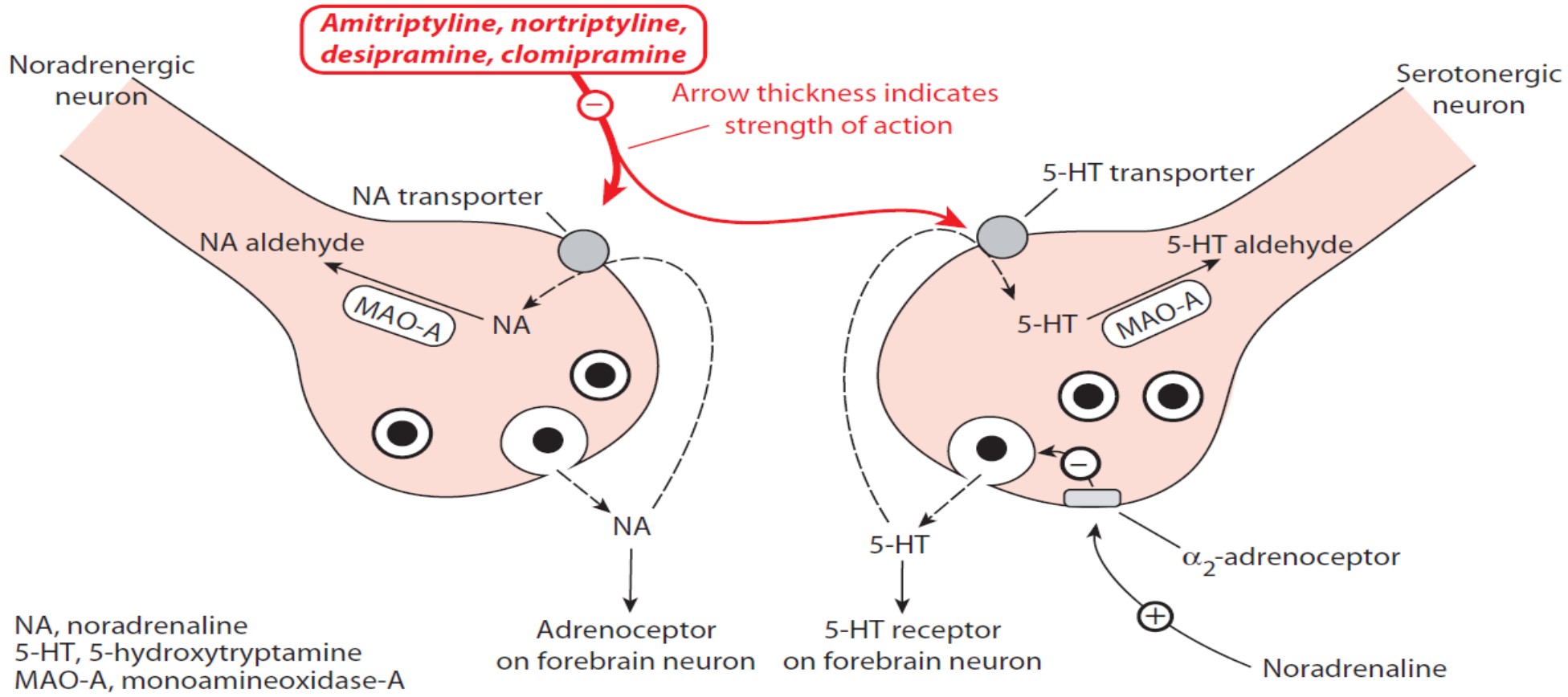
Clinical use Depression. Panic disorder. Neuropathic pain(see set 26). Enuresis.

Adverse effects Sedation (antihistamine action, less with nortriptyline and desipramine). Blurred vision, dry mouth, constipation, urinary retention (antimuscarinic action). Postural hypotension (α_1-adrenoceptor antagonism). Overdose potentially fatal due to cardiac dysrhythmia, severe hypotension, seizure and CNS depression. Not given with MAOIs. Increased risk of suicide in young patients.

R&D 7e Ch 46, pp 574-576; D&H 2e Ch 40, pp 92-93

24.02 **Fluoxetine** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Selective serotonin reuptake inhibitor (SSRI) (Similar drugs: paroxetine, citalopram, escitalopram, sertraline, fluvoxamine)

Fluoxetine

Actions Antidepressant.

MOA Inhibits the reuptake 5-HT into serotonergic neurons, so potentiating transmitter action. The antidepressant action is not seen for a few weeks, because longer-term changes (e.g. down-regulation of receptors) are required for this. (Less marked antimuscarinic and antihistaminergic actions than the TCAs.)

Abs/Distrib/Elim Oral administration. Brain concentration rises over a few days. Hepatic P450 metabolism followed by conjugation reactions. $T_{0.5}$ 1–3 days. Longer-lasting active metabolite. (Half-lives of other SSRIs: paroxetine, 18–24h, fluvoxamine, 18–24h, escitalopram, 24–36h, sertraline, 24–36h.) Strongly bound.

Clinical use Widely prescribed. Depression. Obsessive–compulsive disorder. Panic disorder. Bulimia nervosa.

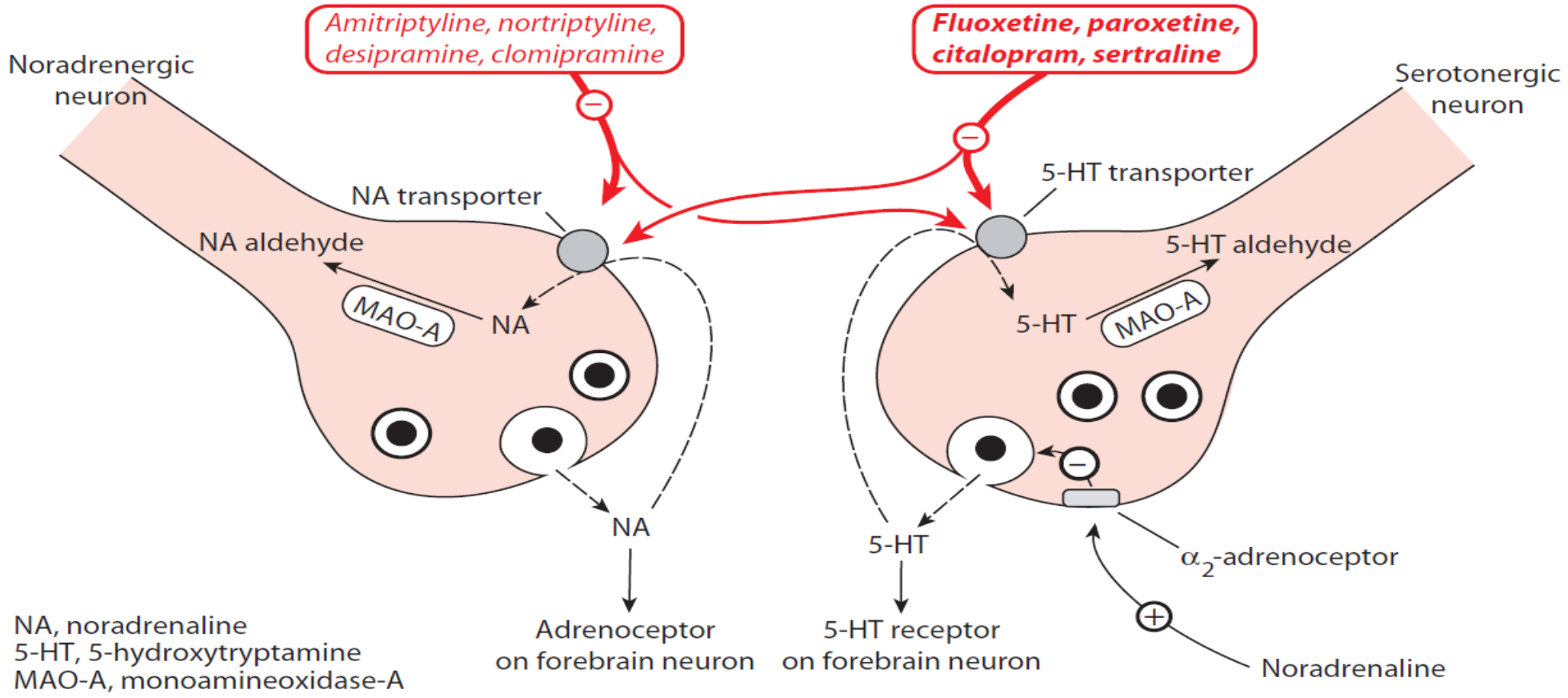
Adverse effects Anxiety and insomnia; can cause nausea, diarrhoea and headache. Sexual dysfunction. Increased risk of suicide in young patients. Not prescribed with MAOIs (risk of serotonin syndrome). Hyponatraemia in elderly. Overdose toxicity much less than for TCAs.

Special points Escitalopram is the active enantiomer of citalopram. Sertraline and escitalopram are the SSRIs which are most selective for 5-HT uptake inhibition.

R&D 7e Ch 46, pp 573-574; D&H 2e Ch 40, pp 92-93

24.03 **Venlafaxine** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



NA, noradrenaline
5-HT, 5-hydroxytryptamine
MAO-A, monoamineoxidase-A

Serotonin/noradrenaline reuptake inhibitor (SNRI) (Similar drug: duloxetine)

Venlafaxine

Actions Antidepressant.

MOA Inhibits the reuptake of noradrenaline into noradrenergic neurons and 5-HT into serotonergic neurons, so potentiating transmitter action. The antidepressant action is not seen until a few weeks later. No important effects on histamine, muscarinic or adrenergic receptors.

Abs/Distrib/Elim Oral administration. Half-life 5h (active metabolite – desmethylvenlafaxine. $T_{0.5}$ 11h) Metabolised in liver by cytochrome P450 system. $T_{0.5}$ of duloxetine 12–24h.

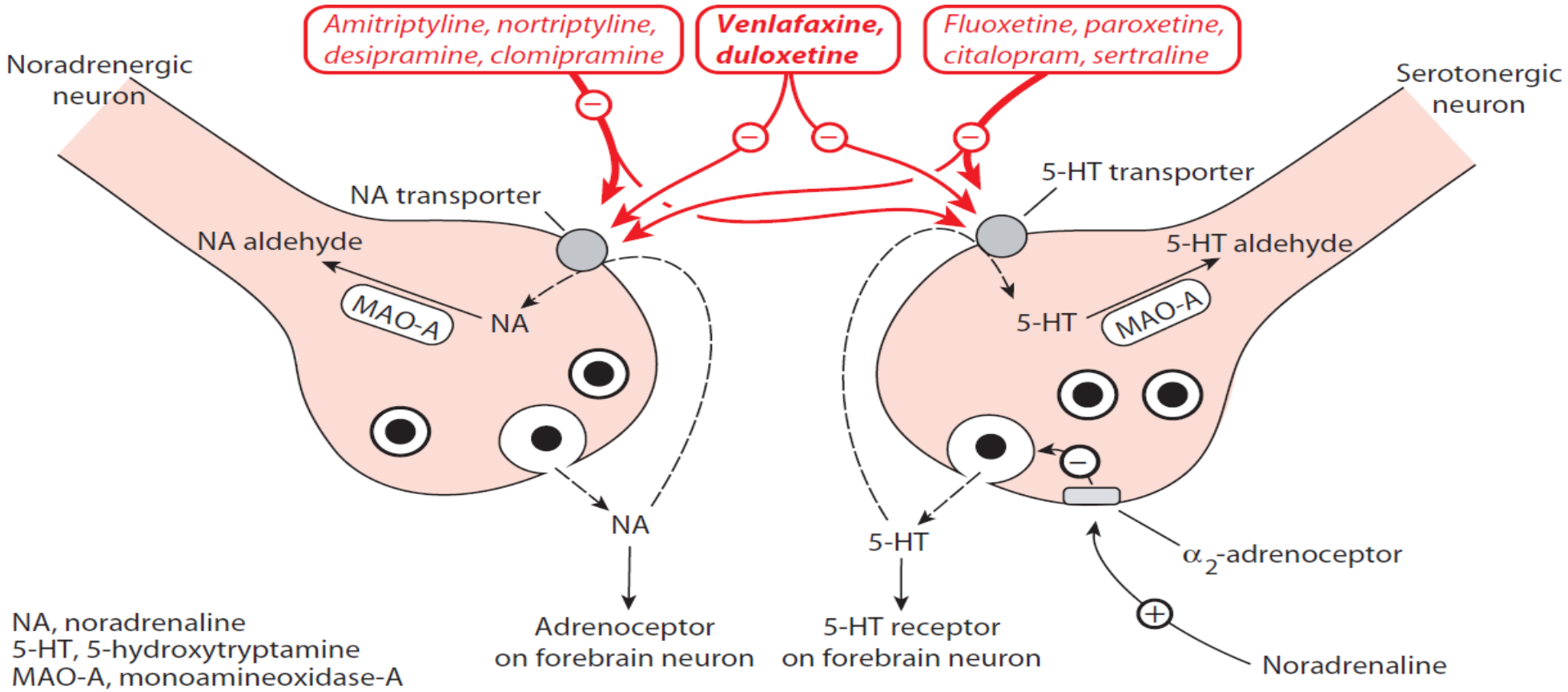
Clinical use Depression (reported to be effective in cases resistant to SSRIs). Panic disorder. Generalised anxiety disorder. Social phobia.

Adverse effects Nausea, headache, sleep problems and sexual dysfunction. Not given with MAOIs (induces serotonin syndrome). Increased risk of suicide in young patients. Overdose causes CNS depression, seizures, cardiac dysrhythmias.

R&D 7e Ch, pp 576-577; D&H 2e Ch 40, pp 92-93

24.04 **Reboxetine** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



Noradrenaline reuptake inhibitor (NRI) (Similar drug: maprotiline)

Reboxetine

Actions Antidepressant.

MOA Inhibits selectively the reuptake of noradrenaline into noradrenergic neurons. (No effect on 5-HT and dopamine transmission.) The antidepressant action is not seen for a few weeks, indicating that other changes (e.g. down-regulation of receptors) are required for the clinical effects.

Abs/Distrib/Elim Oral administration. Metabolised in liver by cytochrome P450 system. Plasma half-life 15h (influenced by P450 inhibitors or inducers).

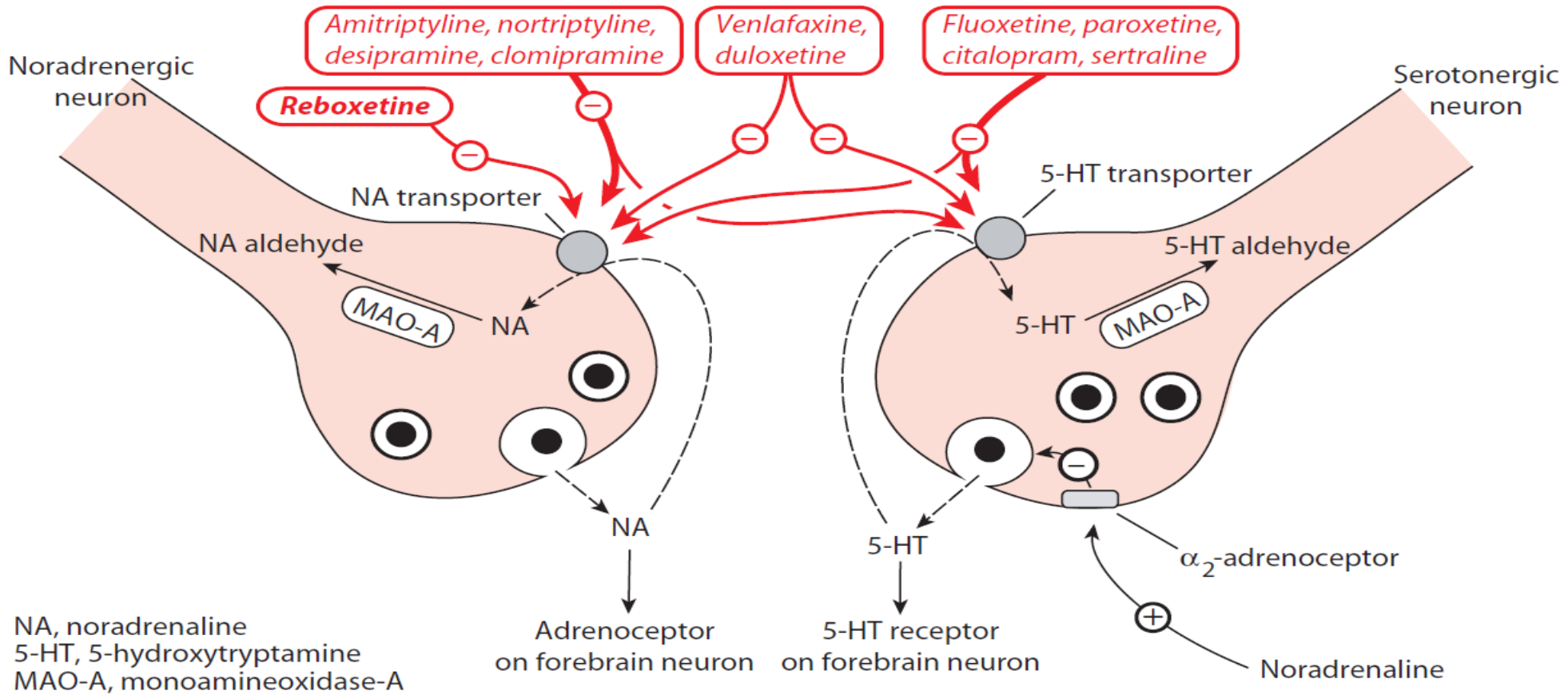
Clinical use Depression. Panic disorder. Proposed for ADHD.

Adverse effects Insomnia, headache, effects due to antagonism of muscarinic and histamine receptors, e.g. sweating, dry mouth, constipation. Unlike SSRIs does not increase risk of suicide in young patients. Maprotiline has similar side effects, consistent with block of receptors, to the TCAs. Not given with MAOIs.

R&D 7e Ch p 577; D&H 2e Ch 40, pp 92-93

24.05 **Phenelzine** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



Monoamine oxidase inhibitor (MAOI) (Similar drugs: isocarboxazid, moclobemide)

Phenelzine

Actions Antidepressant.

MOA Phenelzine and isocarboxacid irreversibly inhibit both the A & B forms of monoamine oxidase. MAO is found in nerve endings, MAO-A acting preferentially on noradrenaline and 5-HT and MAO-B acting mainly on dopamine. MAO inhibition increases the amount of transmitter in the nerve-ending. Antidepressant action is due to MAO-A inhibition. Moclobemide is a selective, reversible inhibitor of MAO-A. (MAO-B inhibitors are used for Parkinson's disease (see card 20.03).)

Abs/Distrib/Elim Oral administration. Plasma half-life 1–2h, but action lasts much longer because of irreversible inhibition of MAO. Moclobemide $T_{0.5}$ 1–2h.

Clinical use Depression; may have particular value for atypical depression. Social phobia. Clinical effect takes some days to develop.

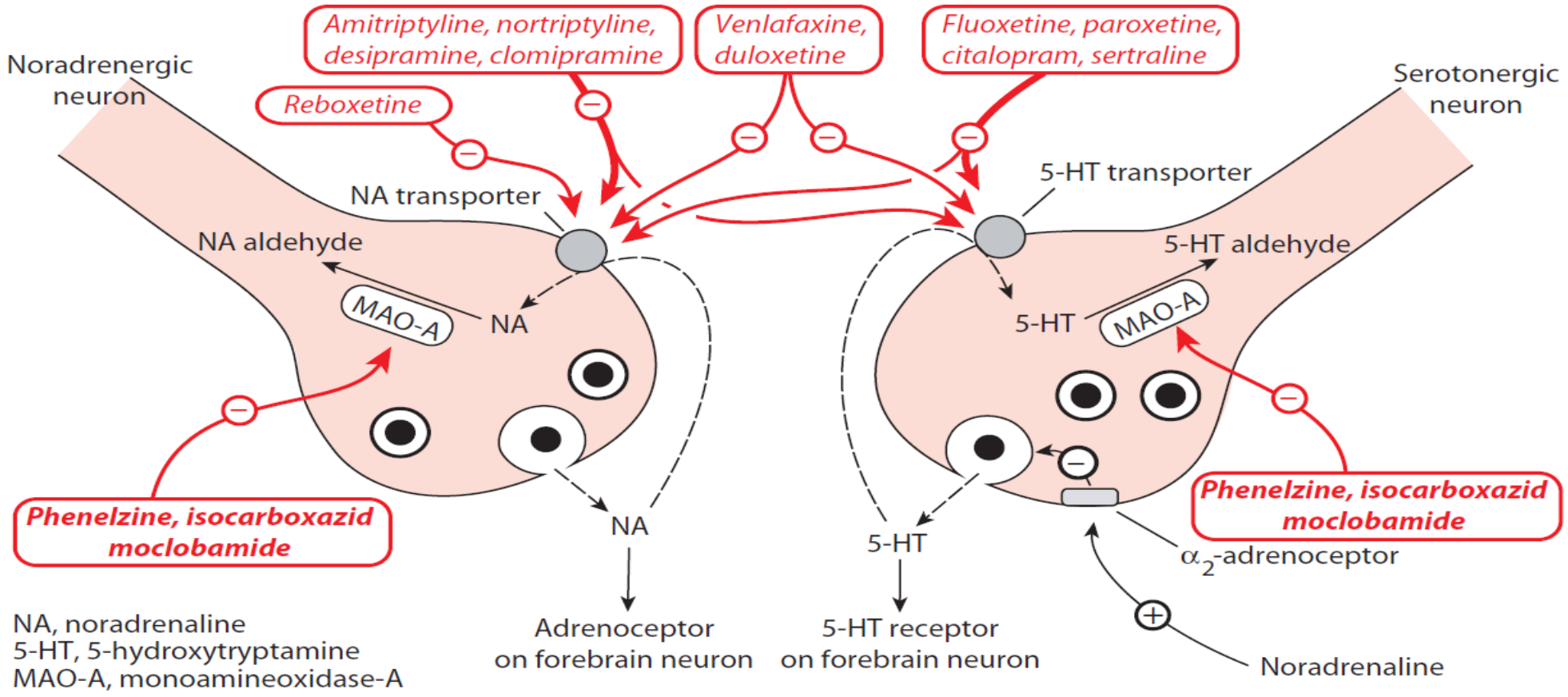
Adverse effects Postural hypotension. Headache. Insomnia. Sexual dysfunction. Dry mouth, urinary retention. Convulsions with overdose. Increased risk of suicide in young patients. Cheese reaction with dietary tyramine – hypertensive crisis. Cheese reaction is less pronounced with moclobemide (since MAO-B is still functional).

Special points Adverse effects are more frequent than with the TCAs or SSRIs so MAOIs are second-line treatment for depression.

R&D 7e Ch 46, pp 577-578; D&H 2e Ch 40, pp 92-93

24.06 **Mirtazapine** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



α-adrenoceptor and 5-HT receptor antagonist

Mirtazapine

Actions Antidepressant.

MOA Antagonist at presynaptic α_2-adrenoceptors so preventing the inhibitory effect of noradrenaline on 5-HT and perhaps also on noradrenaline release from CNS neurons, thus enhancing monoaminergic transmission. Antagonism of 5-HT_2 and 5-HT_3 receptors may be beneficial in reducing side effects due to potentiation of serotonergic transmission (e.g. the sexual dysfunction and nausea produced by uptake inhibitors).

Abs/Distrib/Elim Oral admin. Subject to hepatic cytochrome P450 metabolism. $t_{½}$ 30h. Longer in elderly and those with liver/ renal impairment.

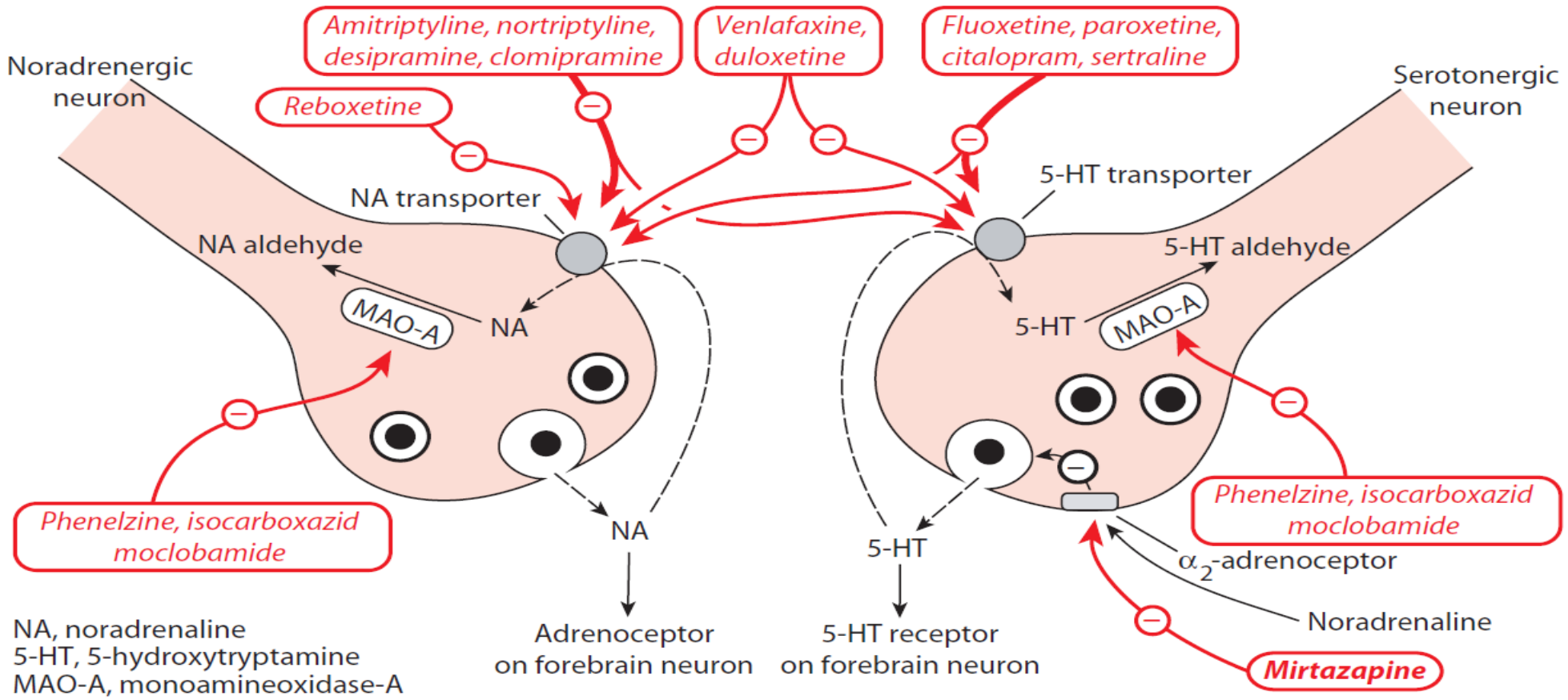
Clinical use Major depression. Post-traumatic stress disorder.

Adverse effects Devoid of many side effects associated with muscarinic or adrenoceptor block, but does have antihistamine actions, e.g. sedation (useful if insomnia accompanies depression). Increased appetite and weight gain. Agranulocytosis is rare but serious.

R&D 7e Ch 46, p 577; D&H 2e Ch 40, pp 92-93

24.07 **Bupropion** Affective disorders – Major Depressive Disorder

Potential sites for antidepressant drug action in noradrenergic and serotonergic neurotransmission in CNS



Bupropion – Dopamine reuptake inhibitor

Bupropion

Actions 'Atypical' antidepressant. Elevates mood.

MOA Relatively selective inhibitor of neuronal dopamine reuptake with a lesser effect on noradrenaline and little effect on 5-HT uptake. Also antagonist at neuronal nicotinic receptors.

Abs/Distrib/Elim Oral admin. Extensive hepatic metabolism by Cyt P450 yields active metabolites which contribute to antidepressant action. $T_{0.5}$ 20h.

Clinical use Alone or in combination with SSRIs for major depression. Also used to help people give up tobacco smoking. Clinical effects take some weeks to develop.

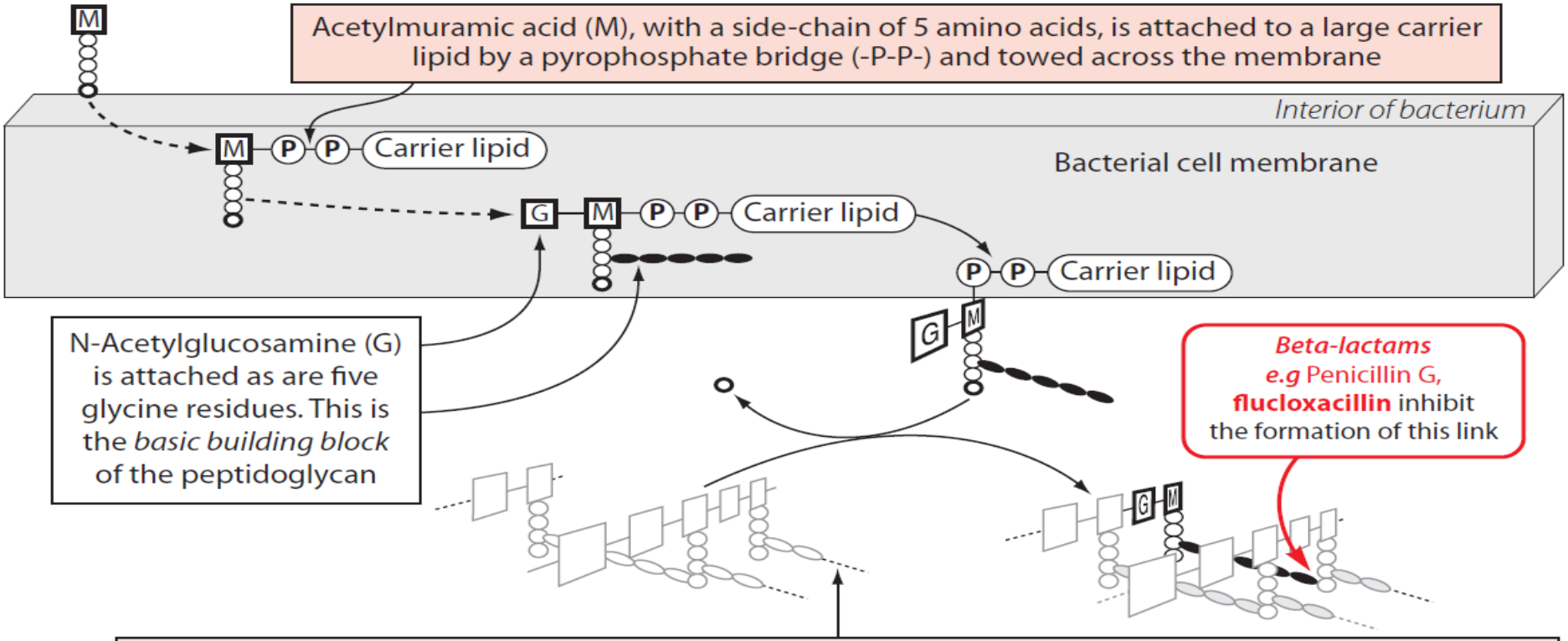
Adverse effects Side effects include: agitation, tremor, dry mouth, nausea, insomnia and skin rashes. It does not cause the weight gain or sexual dysfunction common with other antidepressants. Seizures may be induced with larger doses.

R&D 7e Ch 46, p 577; D&H 2e Ch 40, pp 92-93

Lecture #9 | Drugs used in Meningitis

29.03 **Amoxicillin** Antibacterial agents

Peptidoglycan synthesis and the site of action of drugs



Lecture #9 | Drugs used in Meningitis

A broad-spectrum penicillin antibacterial agent (Similar drug: ampicillin)

Amoxicillin

Actions Bactericidal; interferes with cell wall synthesis in dividing bacteria.

MOA Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed 'building blocks' to the peptidoglycan cell wall backbone.

Special points Inactivated by bacterial β-lactamases; usually given with clavulanic acid which inhibits β-lactamases.

Abs/Distrb/Elim Given i.m. or i.v. or by slow i.v. infusion. Passes into all body fluids; excreted in the urine (blocked by probenecid). Ampicillin is given i.v.

Clinical use Gram-negative bacteria as well as streptococcal, gonococcal, meningococcal infections, anthrax, diphtheria, gas gangrene.

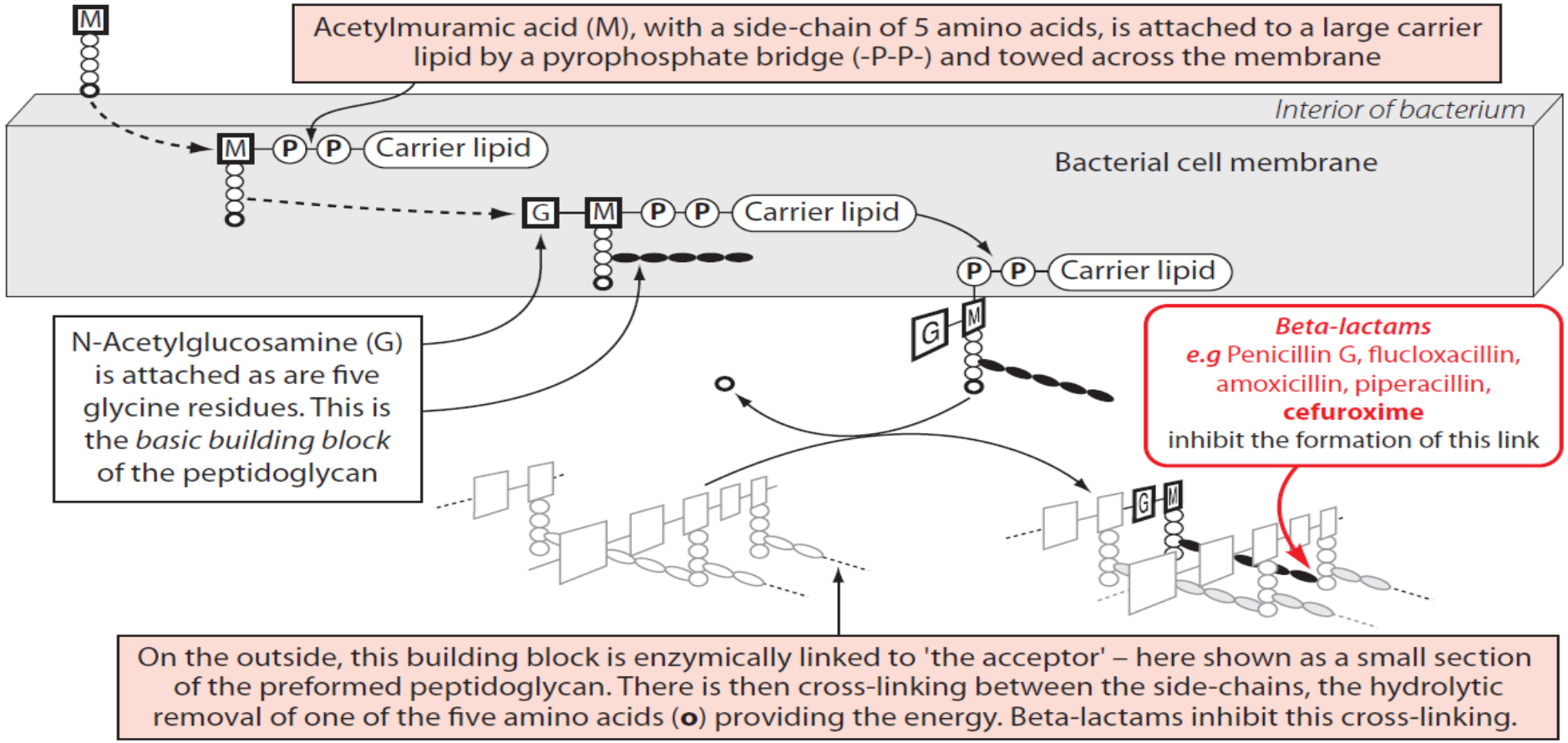
Resistance Not effective against staphylococci (due to β-lactamase) and to streptococci which have impaired β-lactam binding due to mutation of the transpeptidase enzyme.

Adverse effects Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances; rarely colitis.

R&D 7e Ch 50, p 627; D&H 2e Ch 47, pp 107-108

29.06 **Ceftazidime** Antibacterial agents

Peptidoglycan synthesis and the site of action of drugs



A third-generation cephalosporin β-lactam antibiotic

Ceftazidime

Actions Bactericidal; interferes with cell wall synthesis in dividing bacteria.

MOA Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed 'building blocks' to the peptidoglycan cell wall backbone.

Resistance Susceptible to bacterial β-lactamases.

Abs/Distrb/Elim Given by deep i.m. or by i.v. injection or by i.v. infusion. Passes into all body fluids; excreted in the urine (blocked by probenecid). Half-life 1–1.5h.

Clinical use Gram-positive & Gram-negative bacterial and *Pseudomonas aeruginosa* infections.

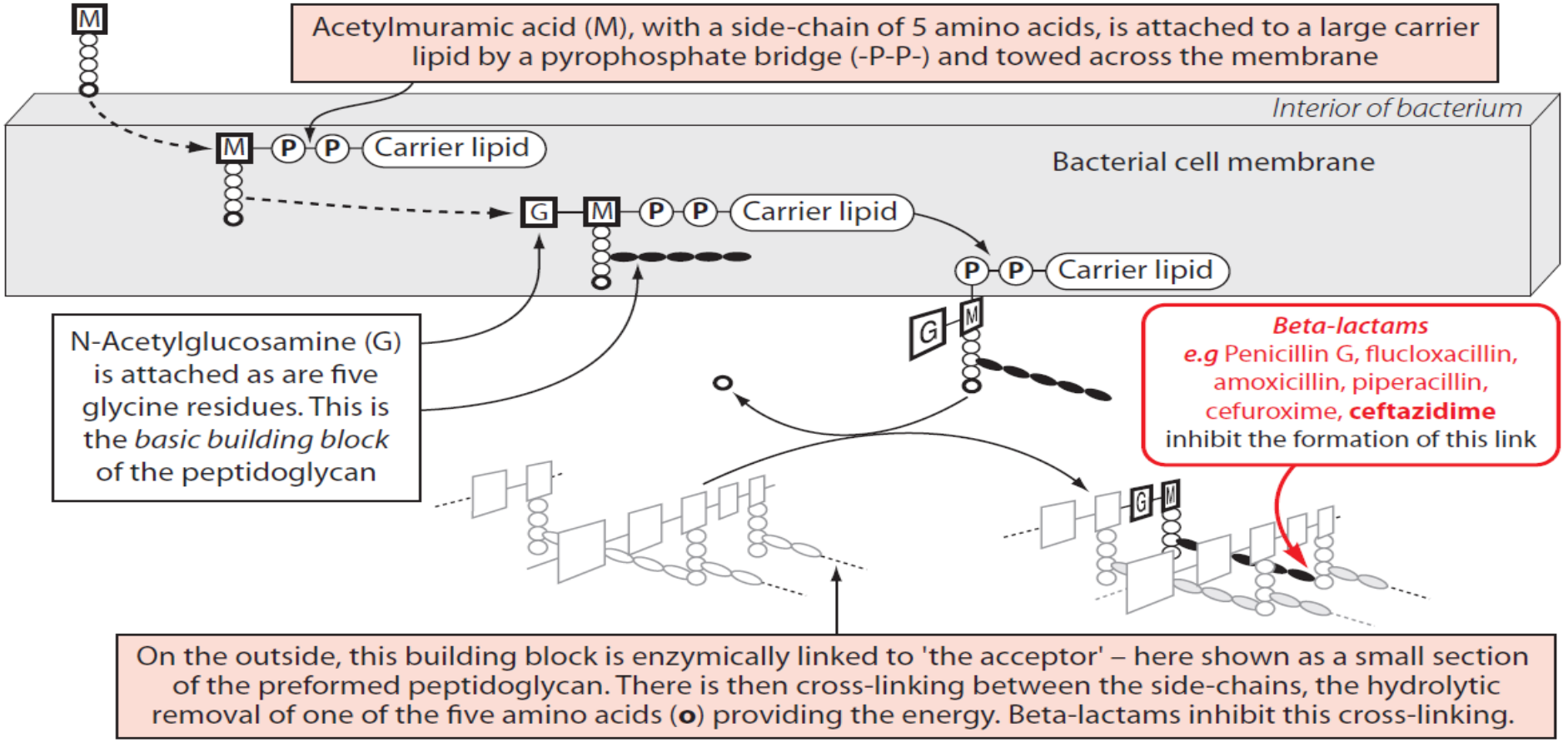
Adverse effects Hypersensitivity reactions (rashes, urticaria, angioedema, fever, arthralgia, anaphylaxis); GIT disturbances, pseudomembranous colitis; superinfection.

Similar drugs Ceftriaxone (half-life 7–8h), cefoperazone (half-life 2h).

R&D 7e Ch 50, p 627-628; D&H 2e Ch 47, pp 107-108

29.07 **Imipenem** Antibacterial agents

Peptidoglycan synthesis and the site of action of drugs



A carbapenem β-lactam antibiotic

Imipenem

Actions Bactericidal; interferes with cell wall synthesis in dividing bacteria.

MOA Binds to and inhibits the enzyme that cross-links the peptide chain of the newly formed 'building blocks' to the peptidoglycan cell wall backbone.

Abs/Distrb/Elim Given by i.v. infusion. Passes into all body fluids including the CSF. Inactivated by renal enzymes so must be given with **cilastatin** which inhibits the relevant enzymes.

Clinical use Broad spectrum: active against Gram-positive, Gram-negative and anaerobic bacteria. Not active against MRSA. Used to treat severe polymicrobial hospital-acquired infections, e.g. septicaemia, pneumonia, complicated urinary infections.

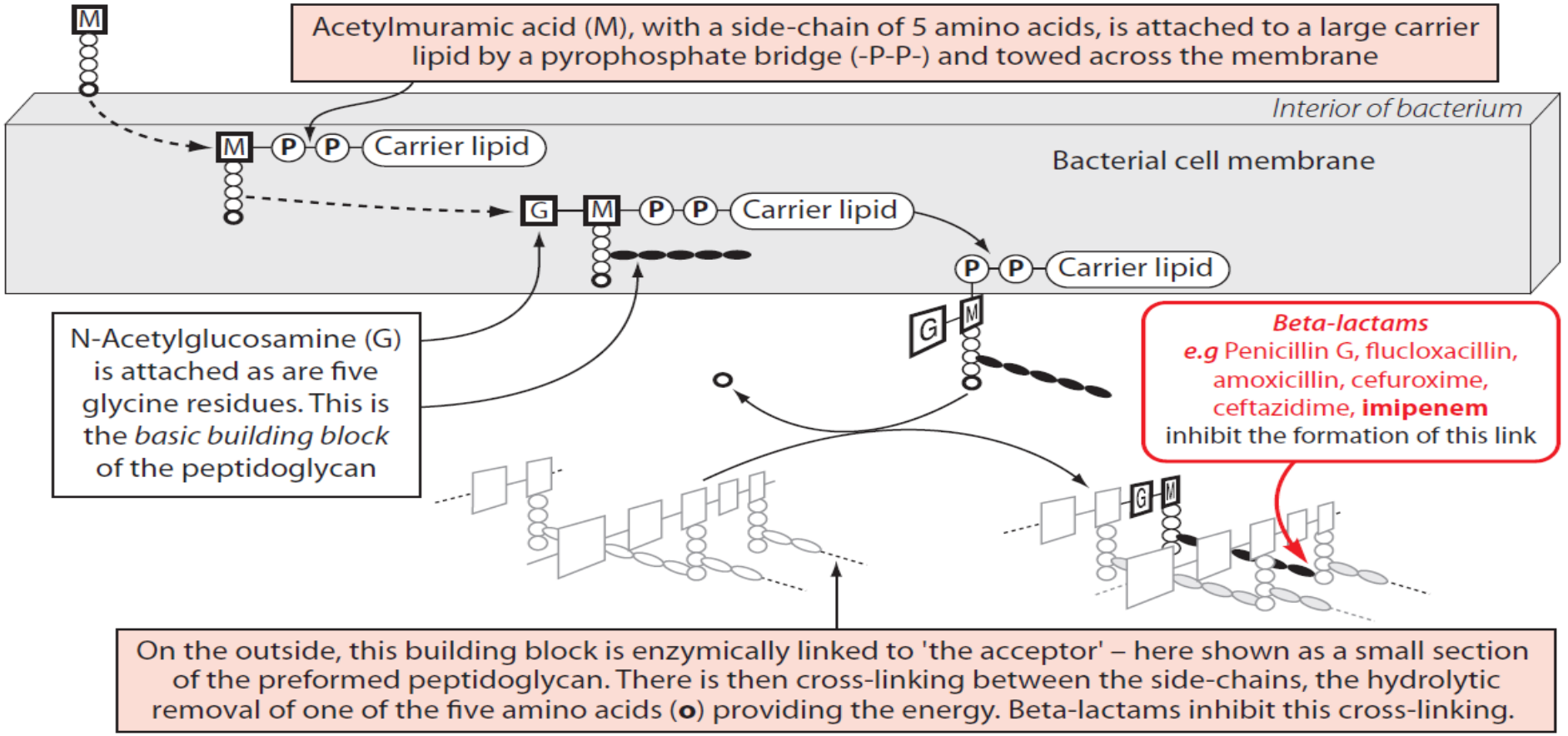
Adverse effects GIT disturbances, rashes, injection site reactions.

Similar drugs Meropenem.

R&D 7e Ch 50, p 628; D&H 2e Ch 47, pp 107-108

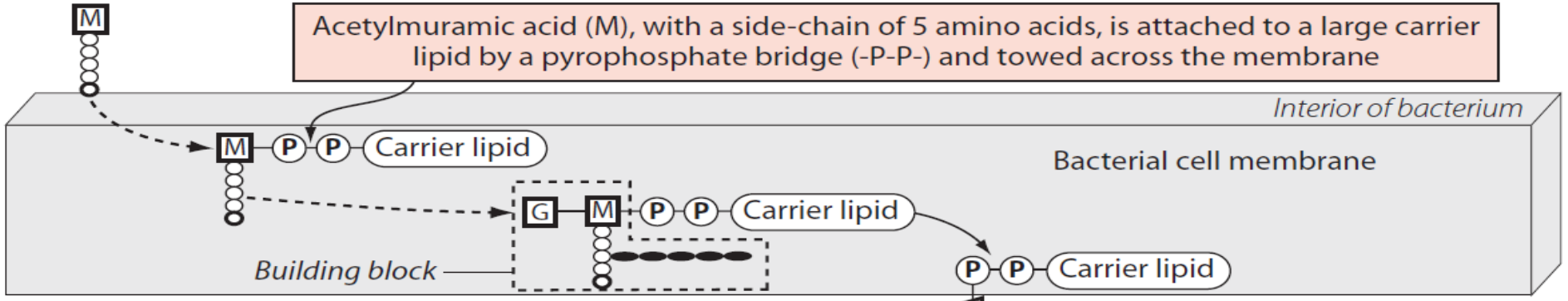
29.08 **Vancomycin** Antibacterial agents

Peptidoglycan synthesis and the site of action of drugs

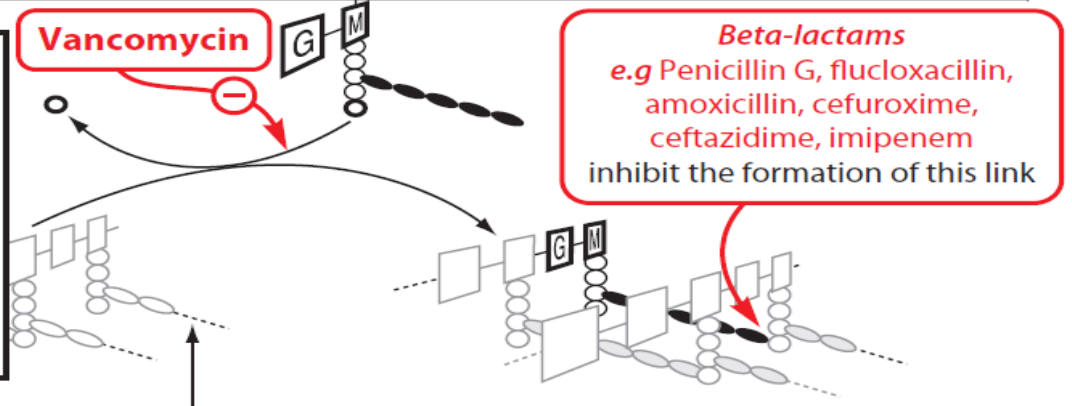


A glycopeptide antibiotic

Vancomycin



Action & MOA	Bactericidal; interferes with cell wall synthesis in dividing bacteria.
Abs/Distrb/ Elim	Given orally for local effect in the mouth,otherwise i-v; renal excretion
Clinical use	MRSA infections, pseudo-membranous colitis
Advers effects	Reversible hearing loss; rarely: renal failure



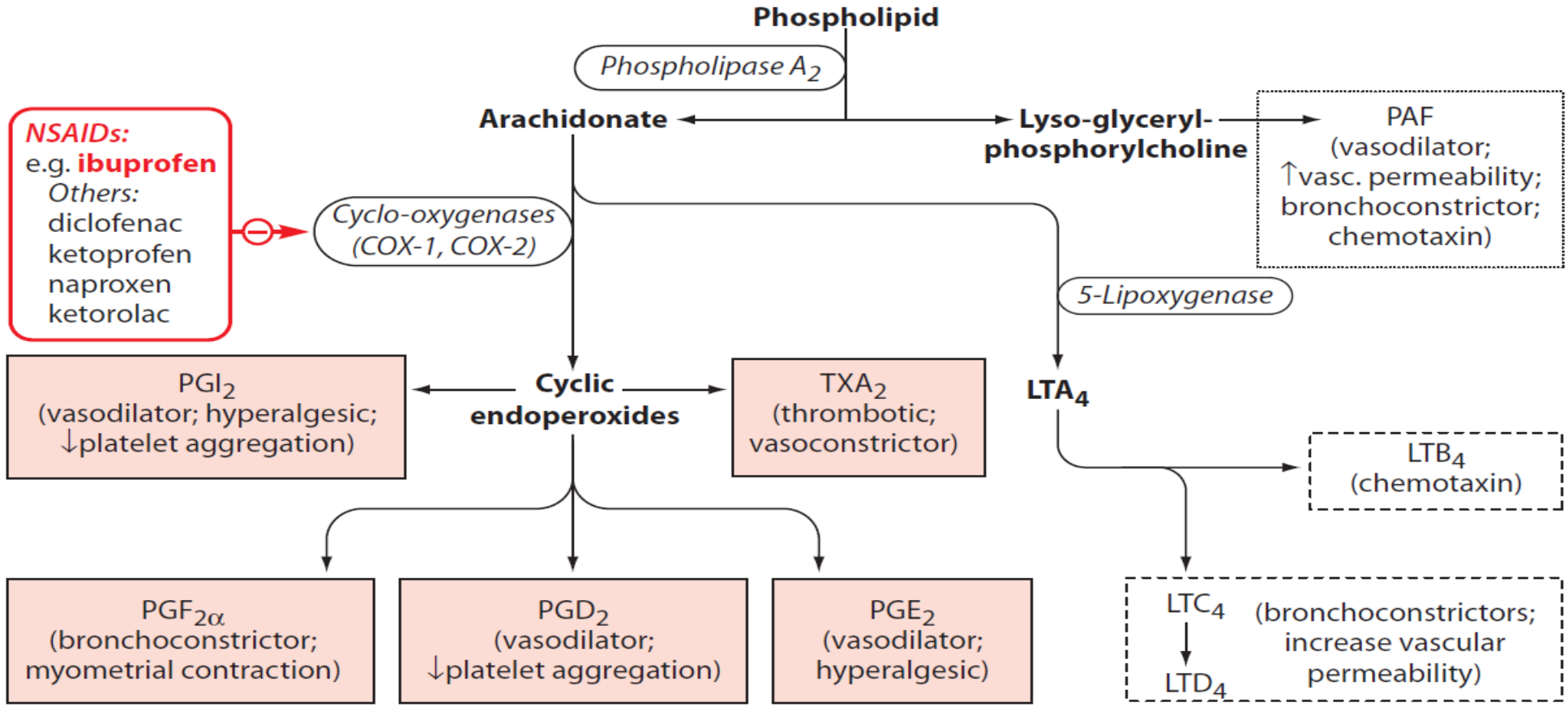
On the outside, this building block is enzymically linked to 'the acceptor' – here shown as a small section of the preformed peptidoglycan. There is then cross-linking between the side-chains, the hydrolytic removal of one of the five amino acids (**o**) providing the energy. **Vancomycin inhibits this removal and thus the attachment of the building block.**

R&D 7e Ch 50, p 628; D&H 2e Ch 47, p 108

Lecture #11 | Drugs Used in Headache and Migraine

3.02 **Aspirin** Inflammation and anti-inflammatory drugs

Mediators of inflammation 1: prostanoids (in grey boxes), leukotrienes (in dashed boxes) and PAF (in dotted box)



A non-steroidal anti-inflammatory drug (NSAID)

Aspirin

Actions Reduces inflammation, is analgesic for inflammatory pain, is antipyretic (i.e. reduces raised temperature). Inhibits platelet aggregation (see card 10.01).

MOA Irreversible acetylation of cyclo-oxygenases; weakly COX-1 selective.

Abs/Distrb/Elim Given orally. Half-life only 30min – rapid hydrolysis to salicylate but effects last longer because the COX has been inactivated and new enzyme must be produced.

Clinical use ***Main use: as antithrombotic in myocardial infarction*** (see card set 7). Other NSAIDs are preferred for anti-inflammatory action and analgesia in musculo-skeletal conditions.

Adverse effects Gastrointestinal disturbances, especially gastric bleeding. In high dosage can cause 'salicylism' (tinnitus, vertigo, reduced hearing); allergic reactions occasionally; renal toxicity rarely. *Can cause the potentially fatal Reye's syndrome (encephalopathy & liver disorder) in children after a viral infection.*

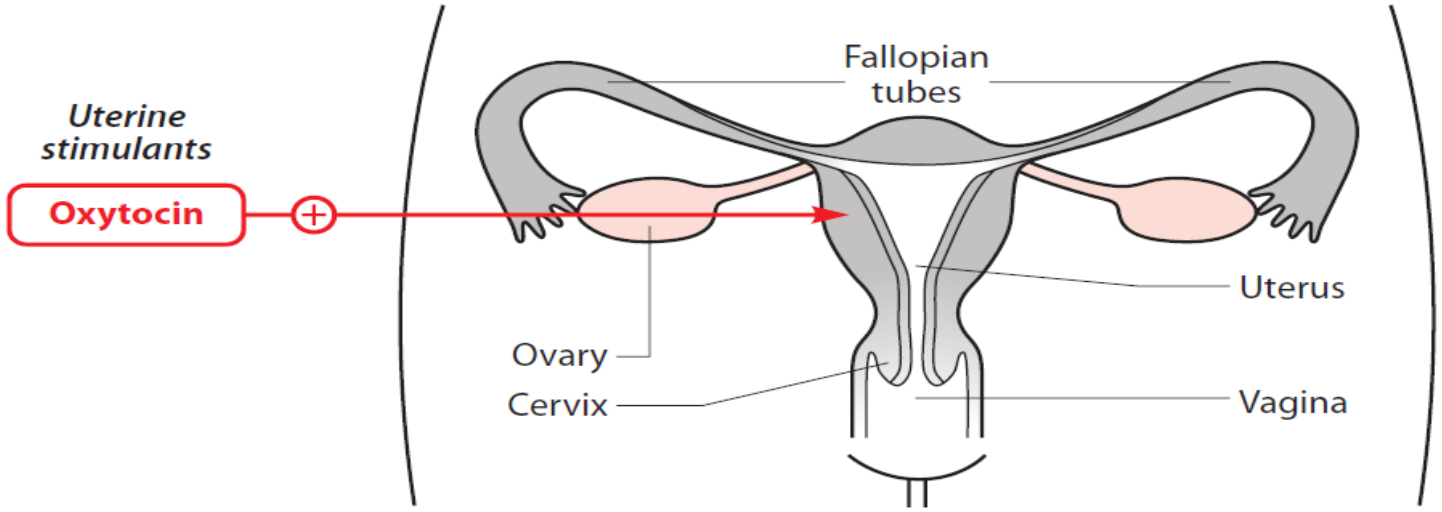
Special points Should not be used in children. Can cause increased effect of warfarin resulting in bleeding. Should not be used for gout because it reduces urate excretion & interferes with the action of uricosuric agents.

R&D 7e Ch 26, pp323-325; D&H 2e Ch 16, pp 42-43

19.05 Ergometrine

Female Reproductive System

The diagram shows a cross-section of the uterus, the Fallopian tubes and the ovaries



Uterine stimulant

Ergometrine

Actions Contracts the relaxed uterus. Has vasoconstrictor action.

MOA Not understood; may act partly on α-adrenoceptors, partly on 5-HT receptors.

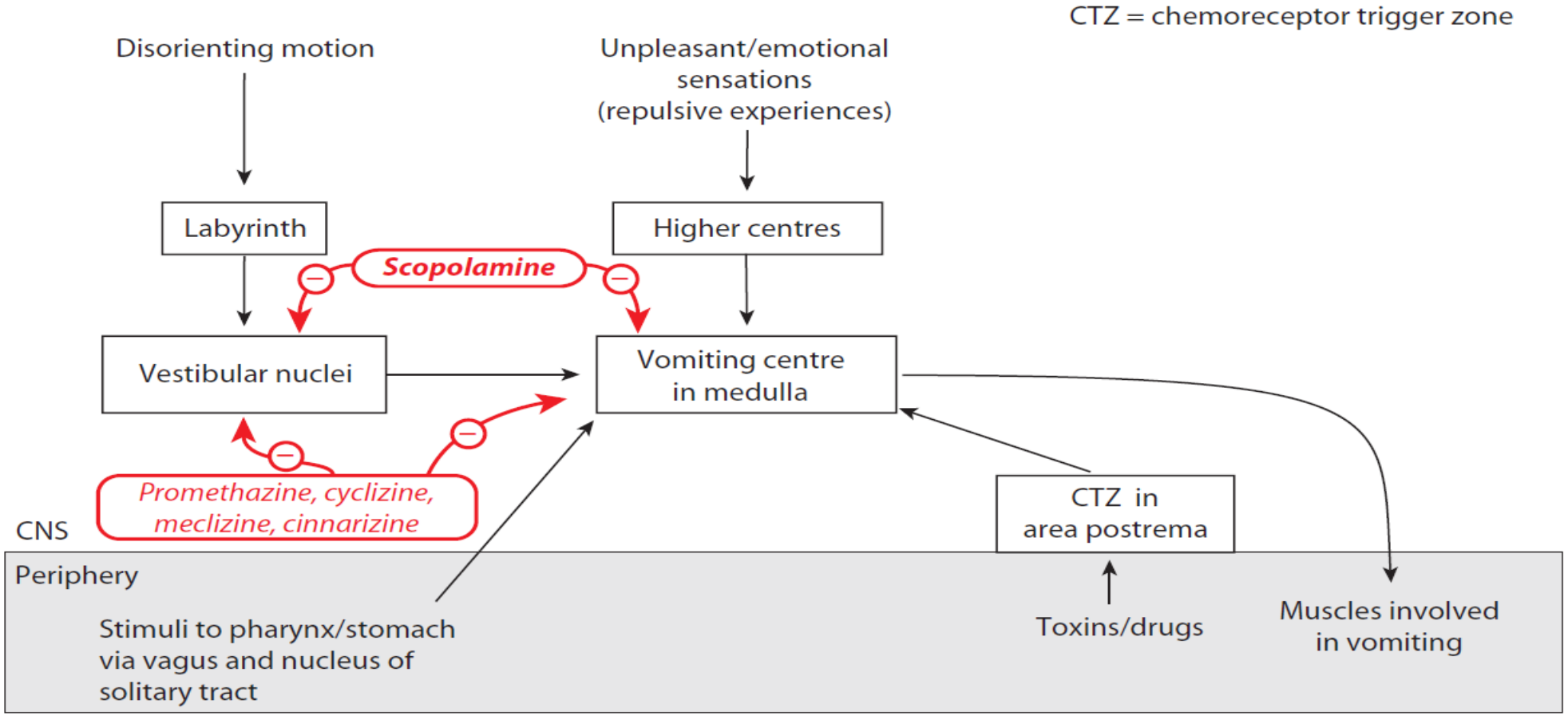
Abs/Distrb/Elim Given orally, i.m. or i.v. Rapid onset of action. Duration: 3–6h.

Clinical use To treat post-partum haemorrhage.

Adverse effects GIT disturbances; increase in BP and in some cases angina (due to vasoconstriction); headache, dizziness; dysrhythmias.

R&D 7e Ch 34, pp 427-428; D&H 2e Ch 32, p 77

The central control of vomiting and stimuli resulting in emesis



5-HT_3-receptor antagonist (Similar drugs: granisetron, dolasetron, tropisetron)

Ondansetron

Actions Antiemetic.

MOA Reversible competitive antagonism at 5-HT_3 receptors in the CTZ and at the sensory endings of vagal afferents in the GIT.

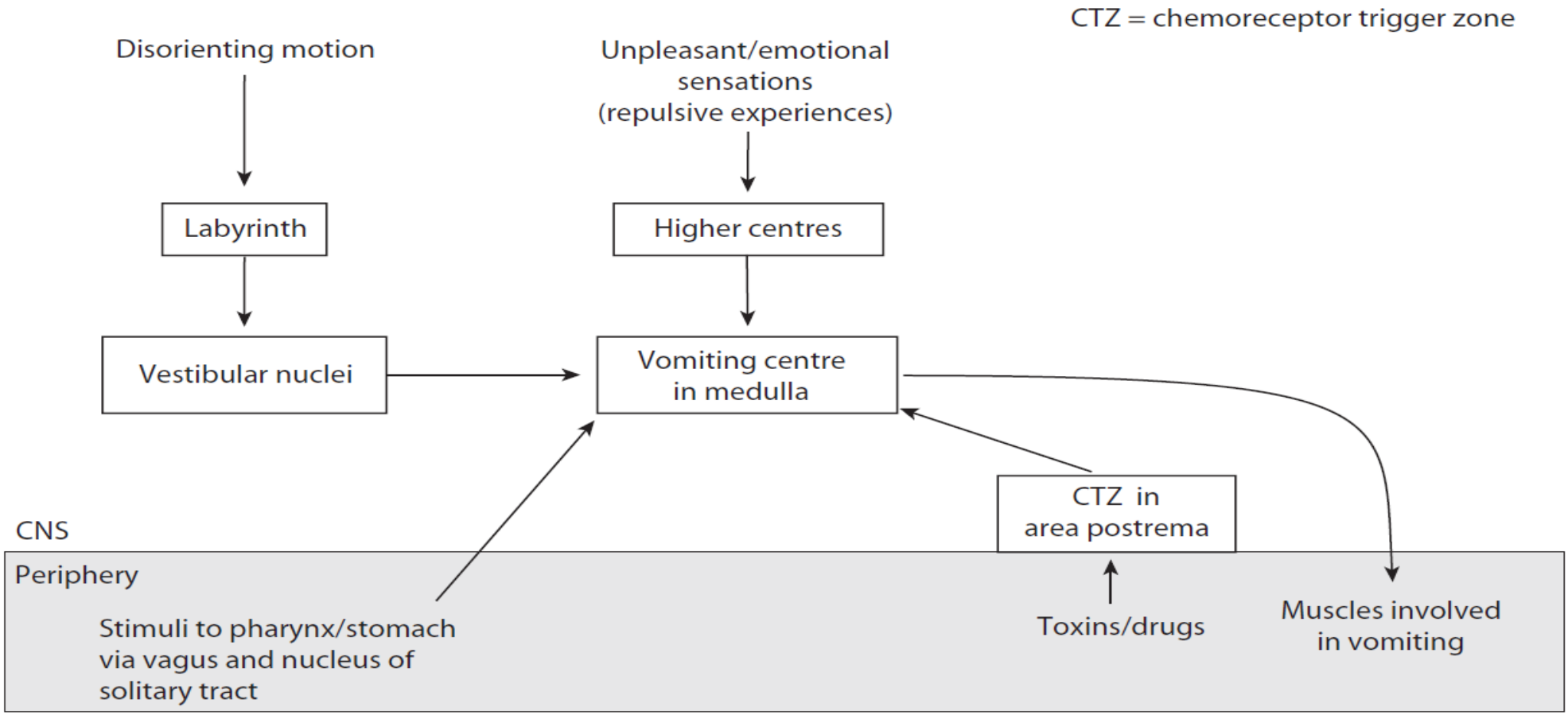
Abs/Distrib/Elim Given orally or i.v. (if vomiting). $T_{0.5}$ 4–6h. Metabolised by cytochrome P450 system in liver.

Clinical use Main agents for nausea and vomiting due to cytotoxic, anticancer drugs. Often given a short time before starting chemotherapy. Nausea and vomiting arising postoperatively or after radiation treatment . Limited effectiveness in motion sickness.

Adverse effects Well tolerated. Headache, GIT upsets.

R&D 7e Ch 29, pp 366-367; D&H 2e Ch 27, p 67

The central control of vomiting and stimuli resulting in emesis



Histamine H_1-receptor antagonist (Similar drugs: cyclizine, meclizine, cinnarizine)

Promethazine

Actions Antiemetic. Sedative. (Also prevents histamine's actions in the periphery, e.g. Use in hay fever (see card 4.07).

MOA Reversible competitive antagonist at H_1 receptors. Antiemetic action is due to blocking H_1 receptors in the vestibular nuclei and in the 'vomiting centre'.

Abs/Distrib/Elim $T_{0.5}$ 10h. Significant first-pass metabolism. Meclizine longer $T_{0.5}$.

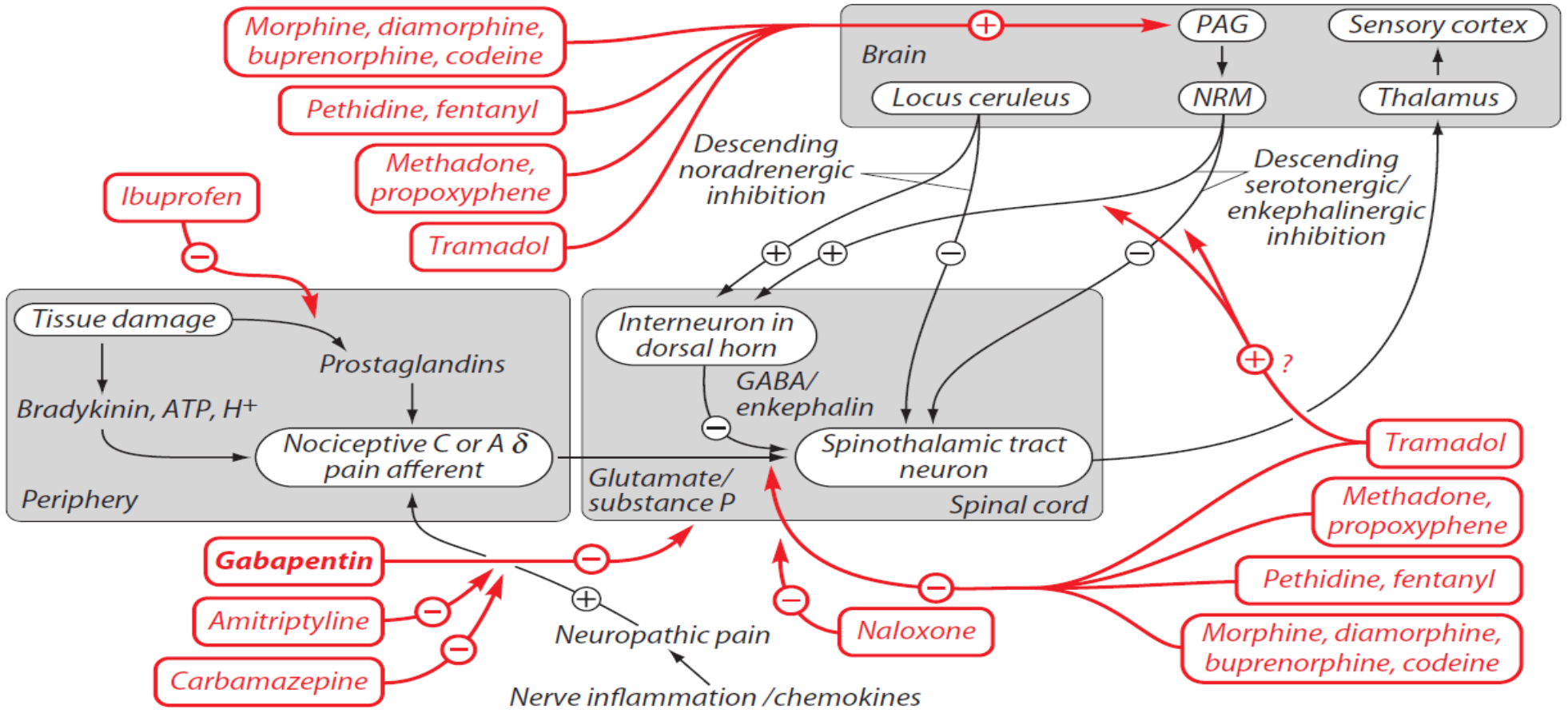
Clinical use Motion sickness and other emesis of vestibular origin (e.g. Meniere's disease). Vomiting in early pregnancy. Emesis due to local stimuli in the gut acting via the vagus.

Adverse effects Sedative action may not be desirable – contraindicated for driving etc. Confusion in elderly. Cyclizine and cinnarizine are less sedating. Dry mouth (anticholinergic action). Potentially fatal respiratory depression in infants under 2y.

R&D 7e Ch 29, p 366; D&H Ch 27, p 67

26.10 **Sumatriptan and the treatment of migraine** Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Antimigraine drug (Similar drugs: zolmitriptan, eletriptan et al.)

Sumatriptan

The pathophysiology of migraine is likely to involve inflammatory vasodilatation in extracerebral cranial blood vessels and stimulation of trigeminal nerve terminals (which might induce further inflammation by the release of neuropeptides).

Treatment of acute attack is with **NSAIDS** (aspirin, ibuprofen, tolfenamic acid, etc.) or **paracetamol**. If this is inadequate, **'triptans'** are used.

Sumatriptan is the standard triptan.

MOA Triptans are agonists at 5-HT_{1B} and 5-HT_{1D} receptors. Activation of 5-HT_{1D} receptors causes vasoconstriction of cranial blood vessels (with little effect on peripheral vessels). They also inhibit trigeminal nerve stimulation and peptide release.

Abs/Distrb/Elim Orally active, but low bioavailability. $T_{0.5}$ 1.5h. May be given s.c. if migraine is accompanied by vomiting.

Clinical use Acute migraine attack. Sumatriptan is also effective in cluster headache.

Adverse effects Sumatriptan has adverse cardiac effects and is contraindicated in heart disease.

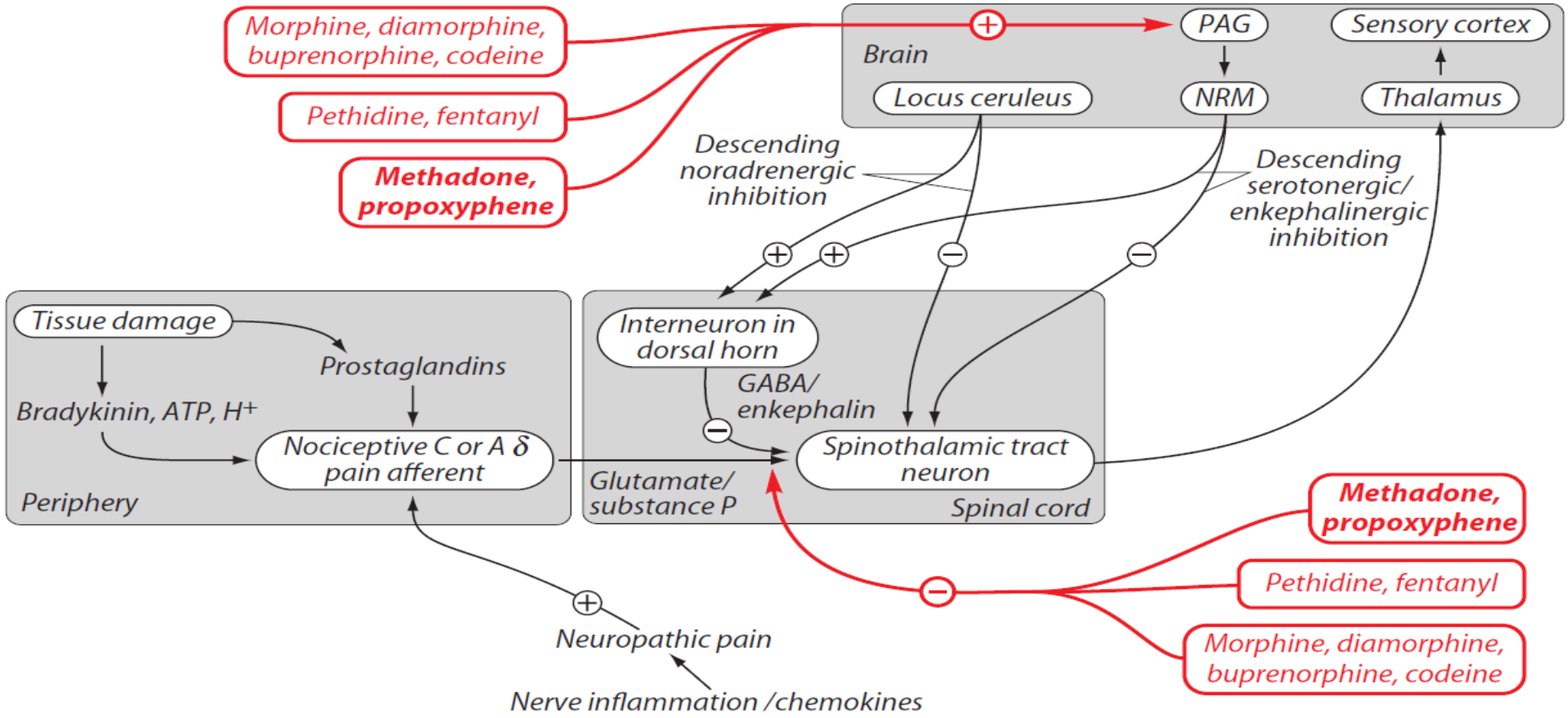
Prophylaxis employs other drugs: β-adrenoceptor antagonists (e.g. propranolol), tricyclic antidepressants (e.g. amitriptyline), some antiepileptics (topiramate, valproate), pizotifen (5-HT_2 receptor antagonist).

R&D 7e Ch 15, pp 201-202; D&H 2e Ch 12, p 36

26.04 Tramadol

Analgesic drugs and the control of pain

Simplified diagram of pain pathway from periphery to brain



Atypical narcotic analgesic

Tramadol

Actions Analgesia.

MOA Weak agonist action at μ opioid receptors but main action is attributed to enhancement of monoamine neurotransmission by inhibition of 5-HT and noradrenaline reuptake into nerve endings. Analgesic action is reported to be inhibited by 5-HT_3 receptor antagonists.

Abs/Distrb/Elim Oral admin. Subject to hepatic demethylation and conjugation, $T_{0.5}$ 6h.

Clinical use Moderate/moderately severe pain. Used post-operatively. Neuropathic pain.

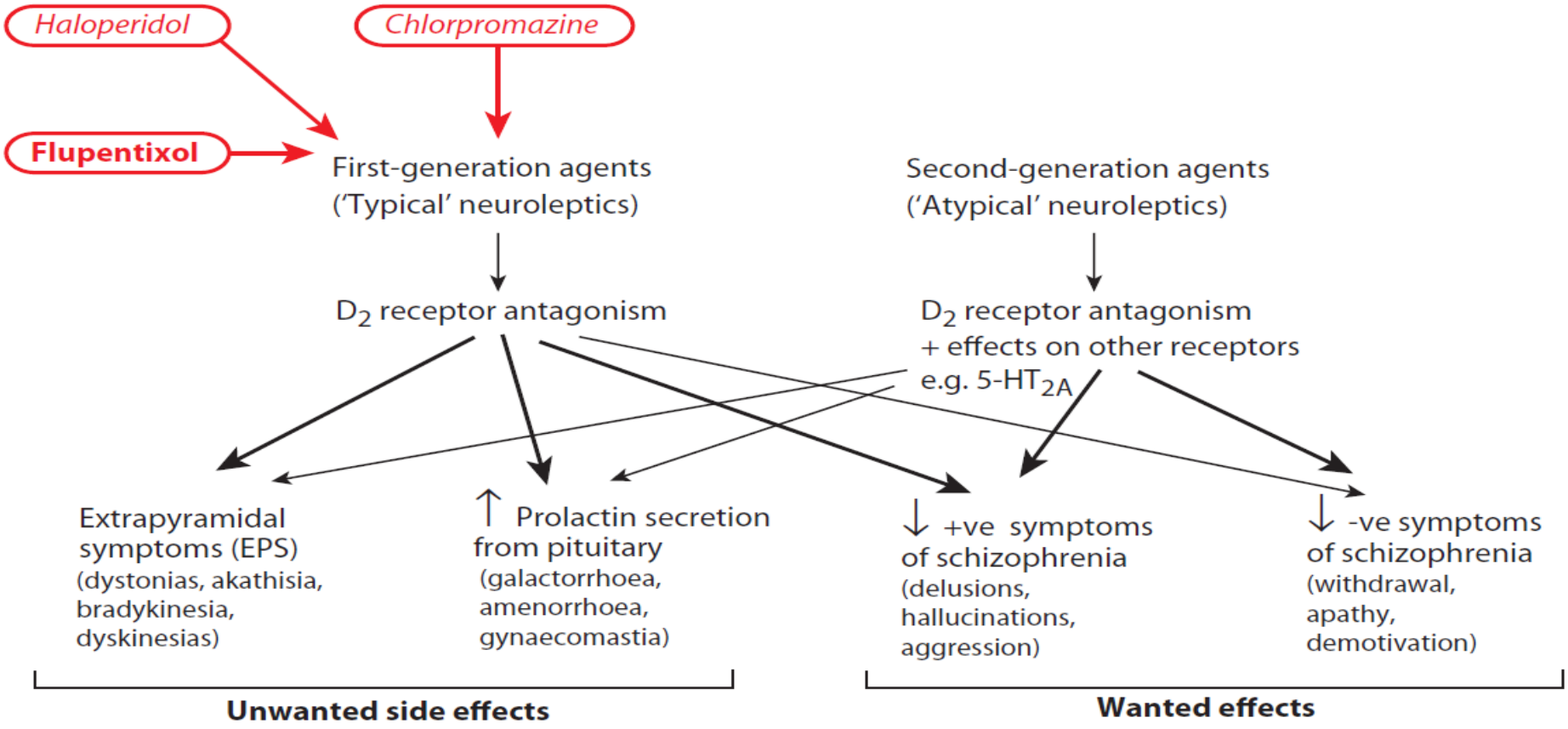
Adverse effects Dizziness, nausea and vomiting. Respiratory depression, constipation and addiction (but less than with morphine). Convulsions.

R&D 7e Ch 41, p 520; D&H 2e Ch 42, p 96

Lecture #12 | Drugs used in schizophrenia

23.04 **Clozapine** Antipsychotics

Diagram illustrating the effects of first- and second-generation antipsychotics



Second-generation ('atypical') antipsychotic drug (Similar drug: olanzapine)

Clozapine

Actions Antipsychotic – effective against +ve and -ve symptoms.

MOA MOA less well established than for typical agents. Action on $5HT_{2A}$ receptors may be important. Antagonist action at muscarinic, $5HT_2$, α_1 adrenoceptors, and H_1 histamine receptors. Higher affinity for D_4 than other dopamine receptors.

Abs/Distrib/Elim Orally active. $t_{½}$ 12h.

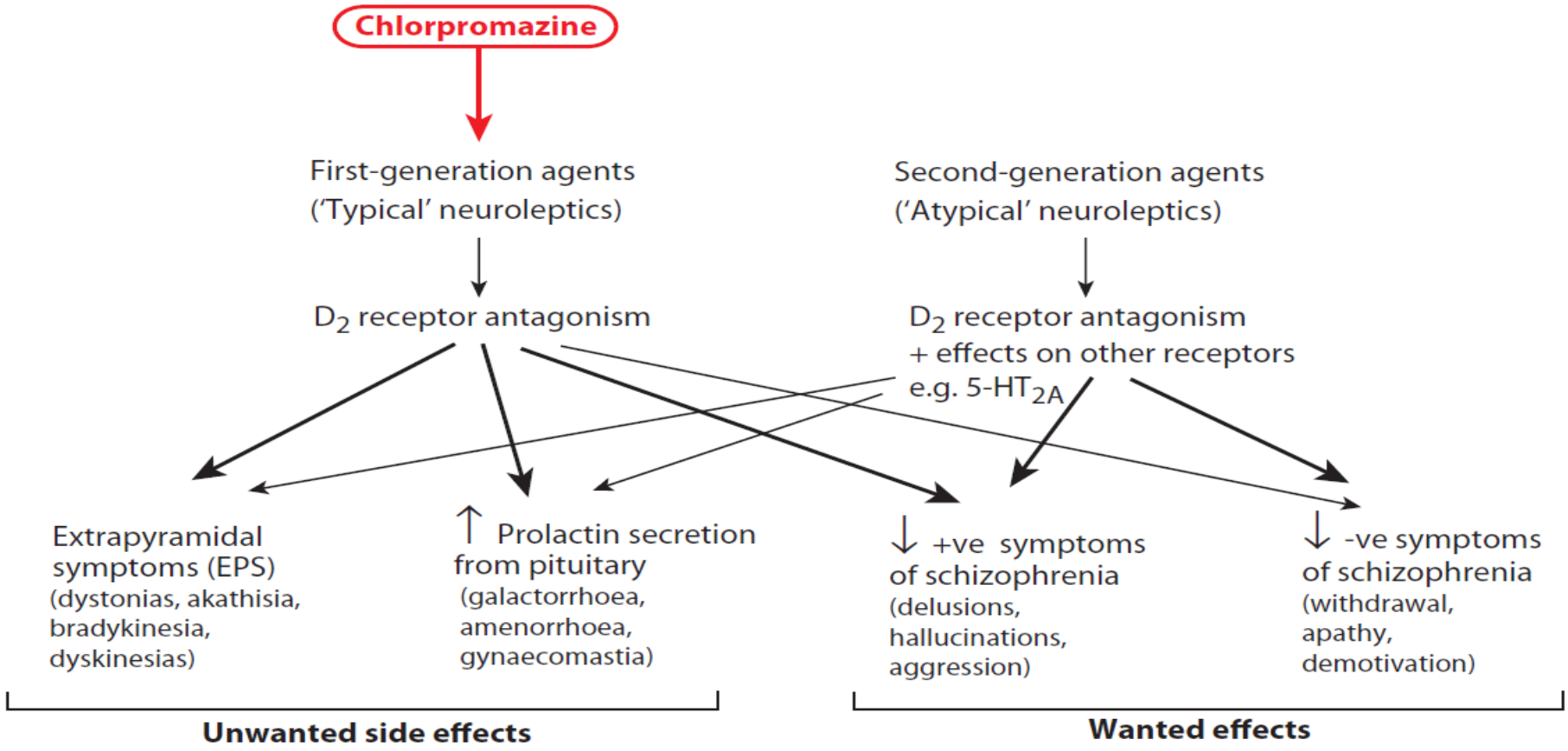
Clinical use Schizophrenia. Because of toxicity, used mainly in patients resistant to other drugs, for whom it is very effective.

Adverse effects Little EPS (reduced D_2 antagonism coupled with antimuscarinic action). Antimuscarinic actions (e.g. constipation). Agranulocytosis (not with olanzapine) – blood testing needed. Sedation. Epileptic seizures. Weight gain (more than with other antipsychotics). Hyperglycaemia.

R&D 7e Ch 45, pp 560-561; D&H 2e Ch 39, pp 90-91

23.02 **Haloperidol** Antipsychotics

Diagram illustrating the effects of first- and second-generation antipsychotics



First-generation, butyrophenone, antipsychotic drug

Haloperidol

Actions Antipsychotic. Apathy. Reduced aggression. Antiemetic

MOA Competitive antagonism of dopamine D_2 receptors in the mesolimbic/mesocortical pathways. Clinical benefits are delayed although receptor block is immediate, suggesting that more complex changes in neurotransmission occur. Higher potency compared to chlorpromazine.

Abs/Distrib/Elim Oral or i.m. admin. (Also i.m. depot.) $t_{½}$ 12–36h.

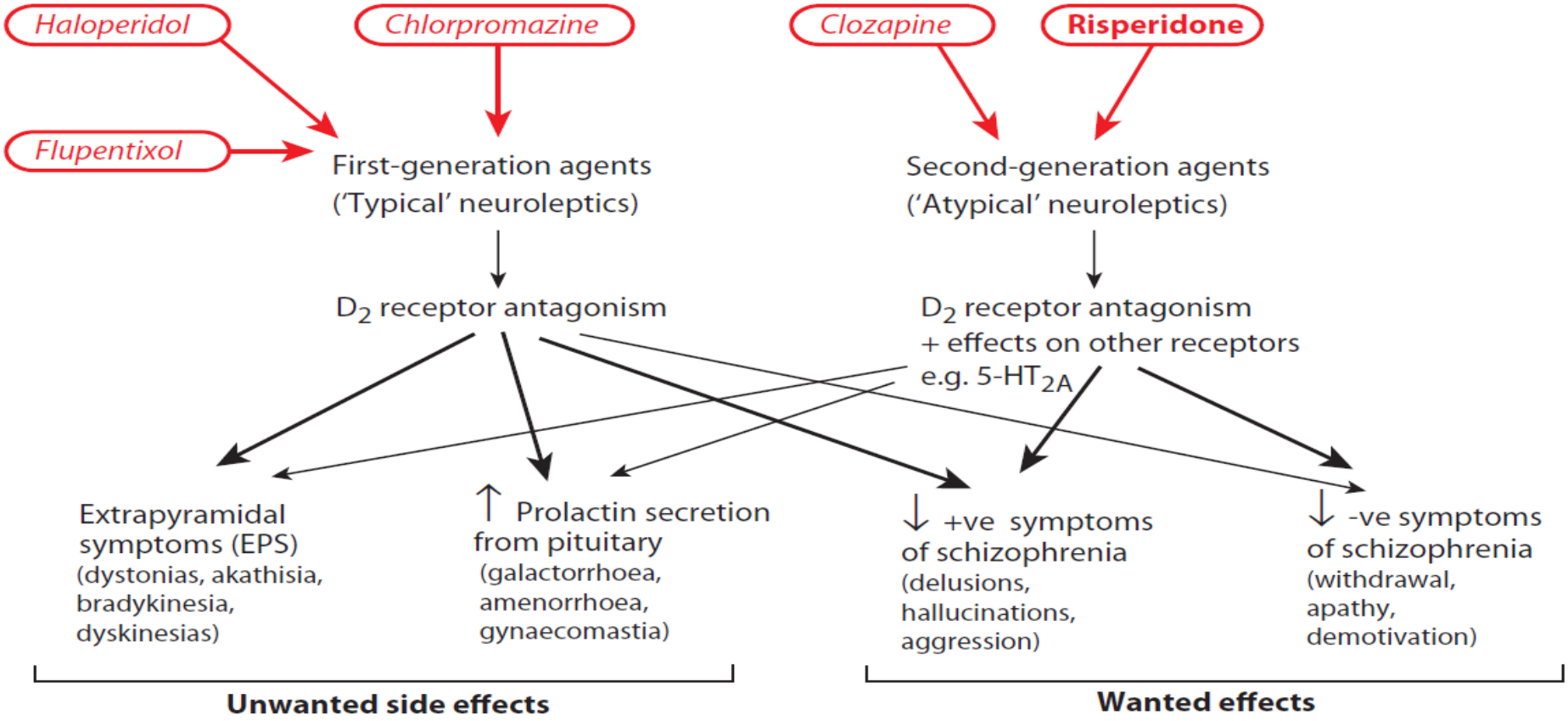
Clinical use Schizophrenia (less effective against negative symptoms) and other psychotic states. Mania. Aggressive behaviour. Tourette's syndrome. Nausea & vomiting. Persistent hiccup.

Adverse effects Marked EPS. Hyperprolactinaemia. Little sedative, hypotensive or antimuscarinic actions. Neuroleptic malignant syndrome.

R&D 7e Ch 45, pp 555-556; D&H 2e Ch 39, pp 90-91

23.06 **Quetiapine** Antipsychotics

Diagram illustrating the effects of first- and second-generation antipsychotics



Second-generation ('atypical') antipsychotic drug

Quetiapine

Actions Antipsychotic. Effective against +ve and -ve symptoms.

MOA Competitive antagonism of dopamine D_2 and $5HT_{2A}$ receptors in the mesolimbic/mesocortical pathways is likely to be important. Antagonism of histamine H_1 receptors may underlie sedative action.

Abs/Distrib/Elim Oral admin. Short (6h) half-life.

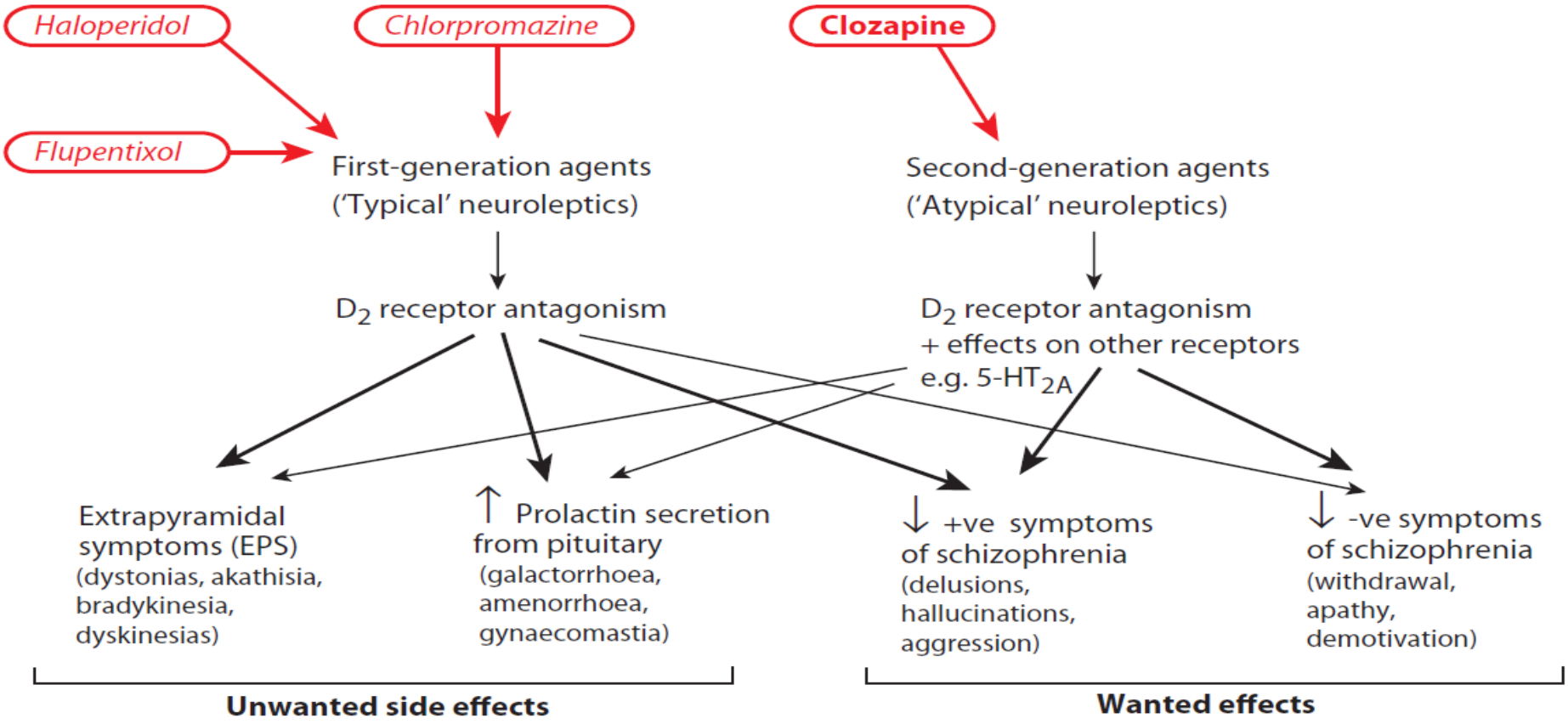
Clinical use Schizophrenia and other psychotic states. Bipolar disorder.

Adverse effects Weight gain. Minor EPS and hyperprolactinaemia. Sedation. Postural hypotension. Constipation, dry mouth (antimuscarinic actions). Rarely, neuroleptic malignant syndrome.

R&D 7e Ch 45, p 557t; D&H 2e Ch 39, pp 90-91

23.05 **Risperidone** Antipsychotics

Diagram illustrating the effects of first- and second-generation antipsychotics



Second-generation ('atypical') antipsychotic drug

Risperidone

Actions Antipsychotic. Effective against +ve and -ve symptoms of schizophrenia.

MOA Potent antagonist of D_2 and $5HT_{2A}$ receptors and α_1 adrenoceptors. As for other atypical agents, a combination of D_2 and $5HT_{2A}$ antagonism may be important in modifying activity in the mesolimbic and mesocortical pathways.

Abs/Distrib/Elim Oral and i.m. depot admin. Hepatic P450 metabolism. $t_{½}$ 3–20h. Active metabolite is longer acting.

Clinical use Schizophrenia and other psychotic states. Manic phase of bipolar disorder.

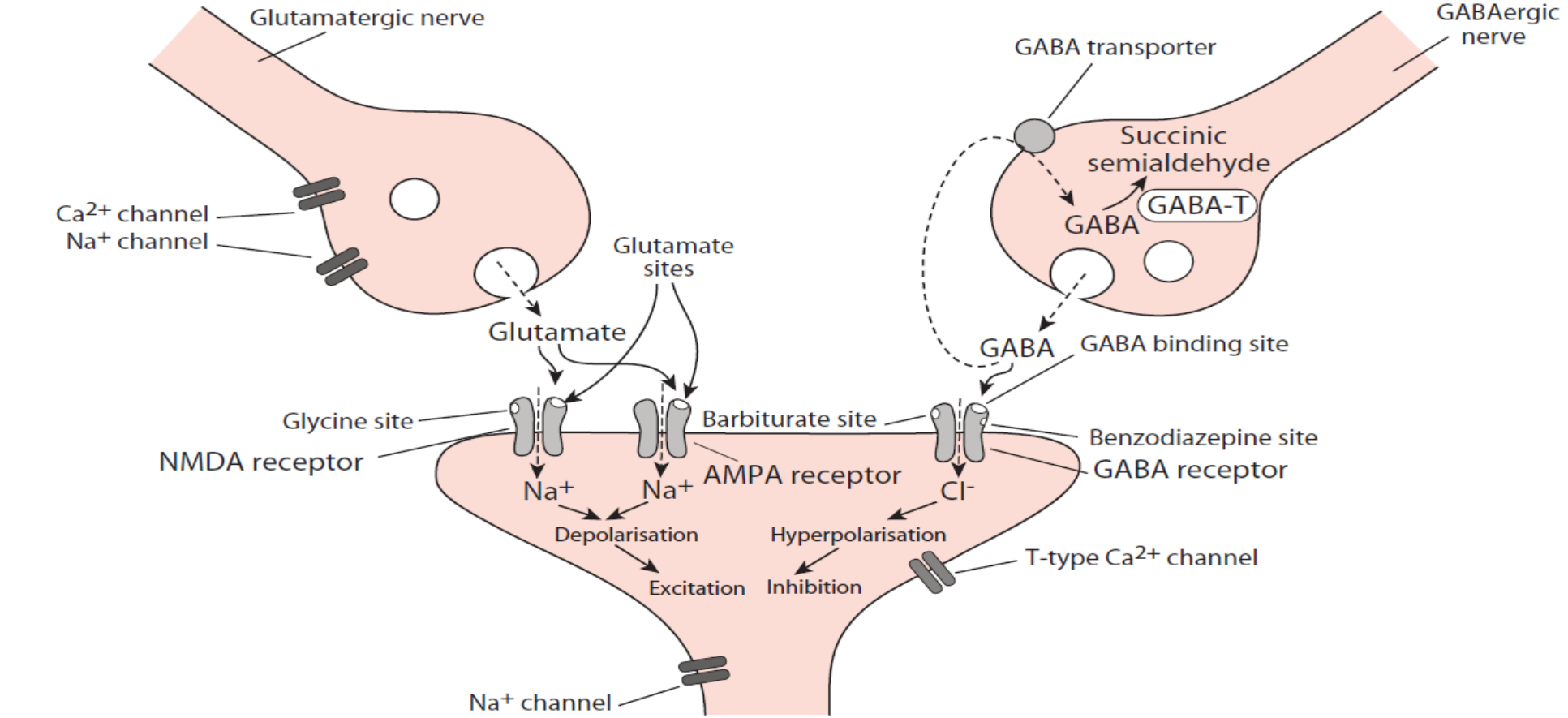
Adverse effects EPS (more than with other atypicals). Insomnia and sedation. Anxiety. Hyperprolactinaemia. Weight gain. Hypotension.

R&D 7e Ch 45, p 557t; D&H 2e Ch 39, pp 90-91

Lecture #13,14 | Drugs for epilepsy

25.01 **Carbamazepine** Antiepileptic drugs

Potential sites of action of antiepileptic drugs



Antiepileptic (Similar drugs: phenytoin, oxcarbazepine)

Carbamazepine

Actions Anticonvulsant. Relieves neuropathic pain.

MOA Blocks Na^+ channels to inhibit action potential initiation and propagation. Use-dependence of block means that action is preferentially on rapidly firing neurons in the epileptic focus.

Abs/Distrib/Elim Oral admin. Metabolised by P450 system in liver to give an active metabolite. $T_{0.5}$ 30h. Phenytoin $T_{0.5}$ 20h but increases with dose due to saturation kinetics.

Clinical use Partial and generalised seizures (tonic-clonic), but not absence seizures. Also neuropathic pain and bipolar disorder. Phenytoin also used for status epilepticus. Saturable elimination of phenytoin makes it useful to monitor its plasma concentration.

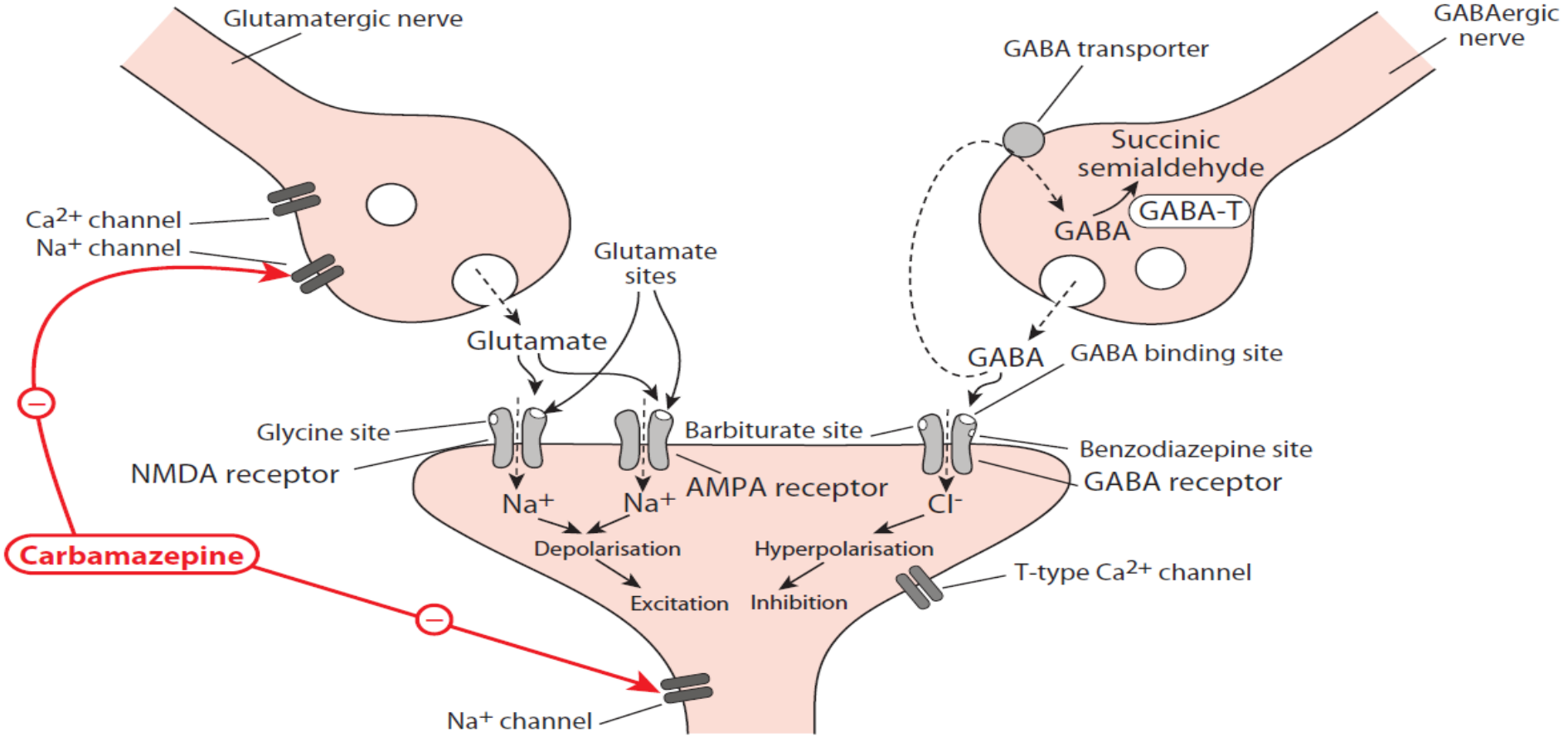
Adverse effects Drowsiness, headache, mental disorientation, motor disturbances. Rare, but serious: liver damage, agranulocytosis, aplastic anaemia, skin reaction. Teratogenic effects (e.g. cleft palate with phenytoin). Phenytoin may cause thickening of the gums and hirsutism.

Special points Induction of cytochrome P450 enzymes causes many drug interactions (e.g. ineffectiveness of oestrogenic contraceptives). Oxcarbazepine much weaker P450 inducer.

R&D 7e Ch 44, p 546; D&H 2e Ch 41, pp 94-95

25.02 **Ethosuximide** Antiepileptic drugs

Potential sites of action of antiepileptic drugs



Antiepileptic

Ethosuximide

Actions Anticonvulsant with specific action on absence seizures.

MOA Blocks T-type Ca^{2+} channels in thalamic neurons to counteract the slow (3Hz), spike and wave, firing pattern thought to be important in absence epilepsy.

Abs/Distrib/Elim Oral admin. Oxidised by cytochrome P450 system. $T_{0.5}$ 50h.

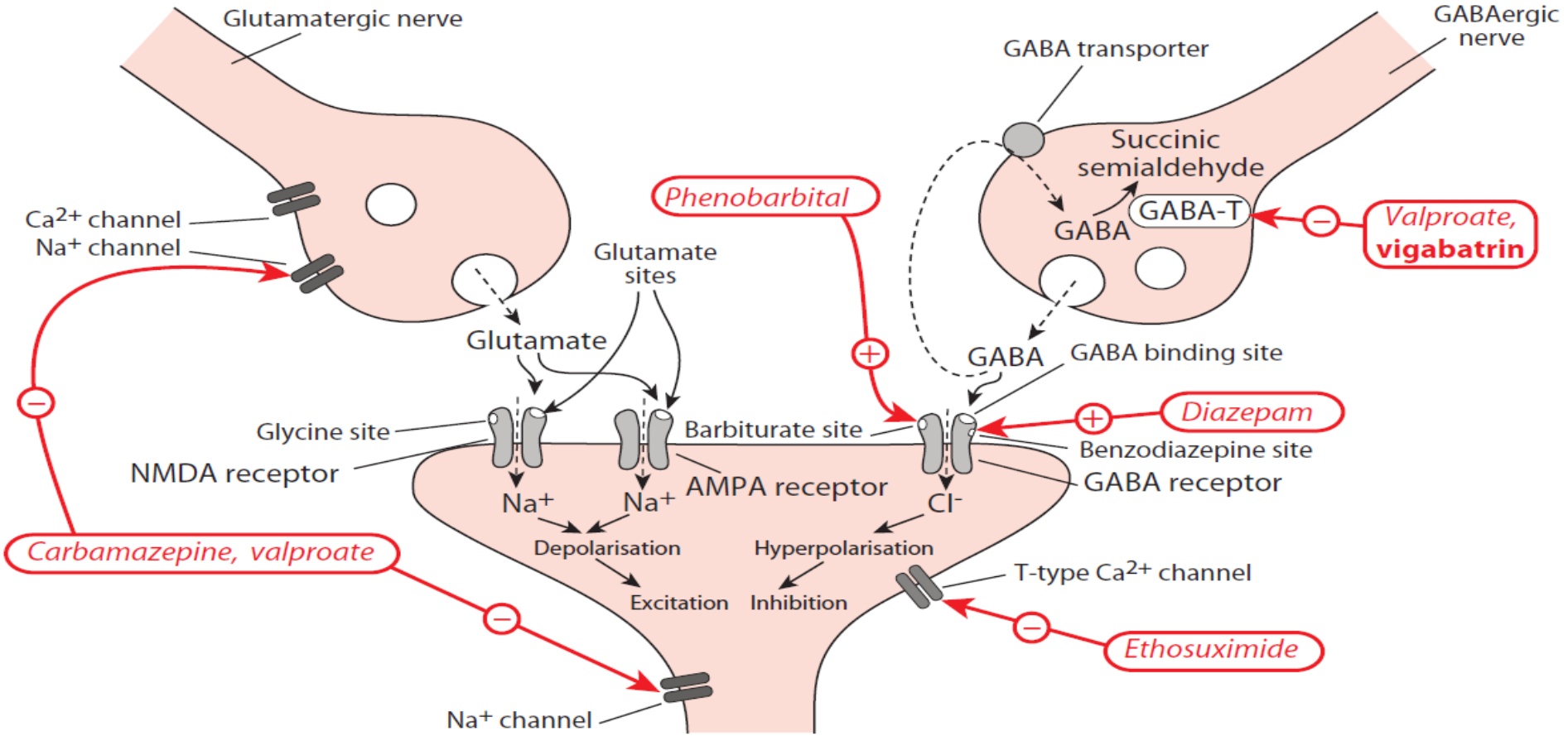
Clinical use Drug of choice for absence seizures (not effective against partial or tonic-clonic seizures).

Adverse effects Anorexia, GIT upset, pancytopaenia. Rash, drowsiness, fatigue. Overdose can cause coma and respiratory depression.

R&D 7e Ch 44, p 548; D&H 2e Ch 41, pp 94-95

25.07 **Lamotrigine** Antiepileptic drugs

Potential sites of action of antiepileptic drugs



Antiepileptic

Lamotrigine

Actions Anticonvulsant. Reduces frequency of mood episodes in bipolar disorder.

MOA Inhibition of glutamate release decreases postsynaptic neuronal excitation. This may be due to Na^+ (and perhaps Ca^{2+}) channel inhibition in the nerve ending.

Abs/Distrib/Elim Oral admin. Subject to hepatic glucuronidation. $T_{0.5}$ 24–36h.

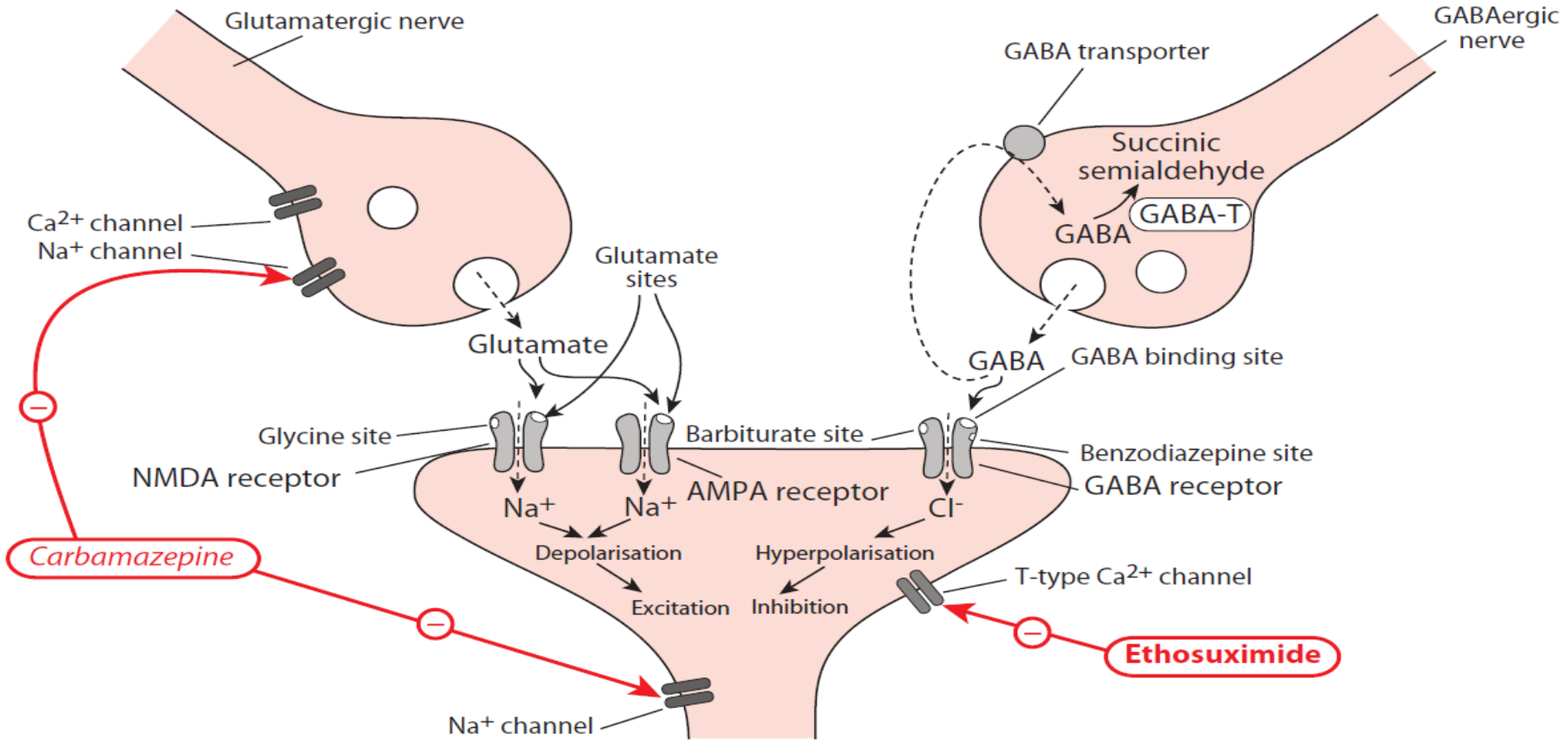
Clinical use Partial and generalised seizures, including absence. Bipolar disorder.

Adverse effects Dizziness, headache, double vision and sedation. Serious skin rashes may occur in a small percentage of patients, particularly children.

R&D 7e Ch 44, p 549; D&H 2e Ch 41, pp 94-95

25.03 **Valproate** Antiepileptic drugs

Potential sites of action of antiepileptic drugs



Antiepileptic

Valproate

Actions Anticonvulsant. Mood stabiliser.

MOA Several actions may contribute to the antiepileptic action: block of voltage-gated Na^+ channels to inhibit action potential initiation and propagation; inhibition of GABA transaminase to reduce GABA breakdown; various effects on second messenger pathways.

Abs/Distrib/Elim Oral admin. Subject to glucuronidation and mitochondrial oxidation. $T_{0.5}$ 9–16h.

Clinical use Most forms of epilepsy (esp. useful in myoclonic seizures). Manic phase of bipolar disorder. Migraine.

Adverse effects Nausea & vomiting. Tremor. Weight gain. Reproductive dysfunction. Hepatic (especially in infants) and pancreatic toxicity. Teratogenic effects (e.g. neural tube defects including spina bifida).

R&D 7e Ch 44, pp 547-548; D&H 2e Ch 41, pp 94-95