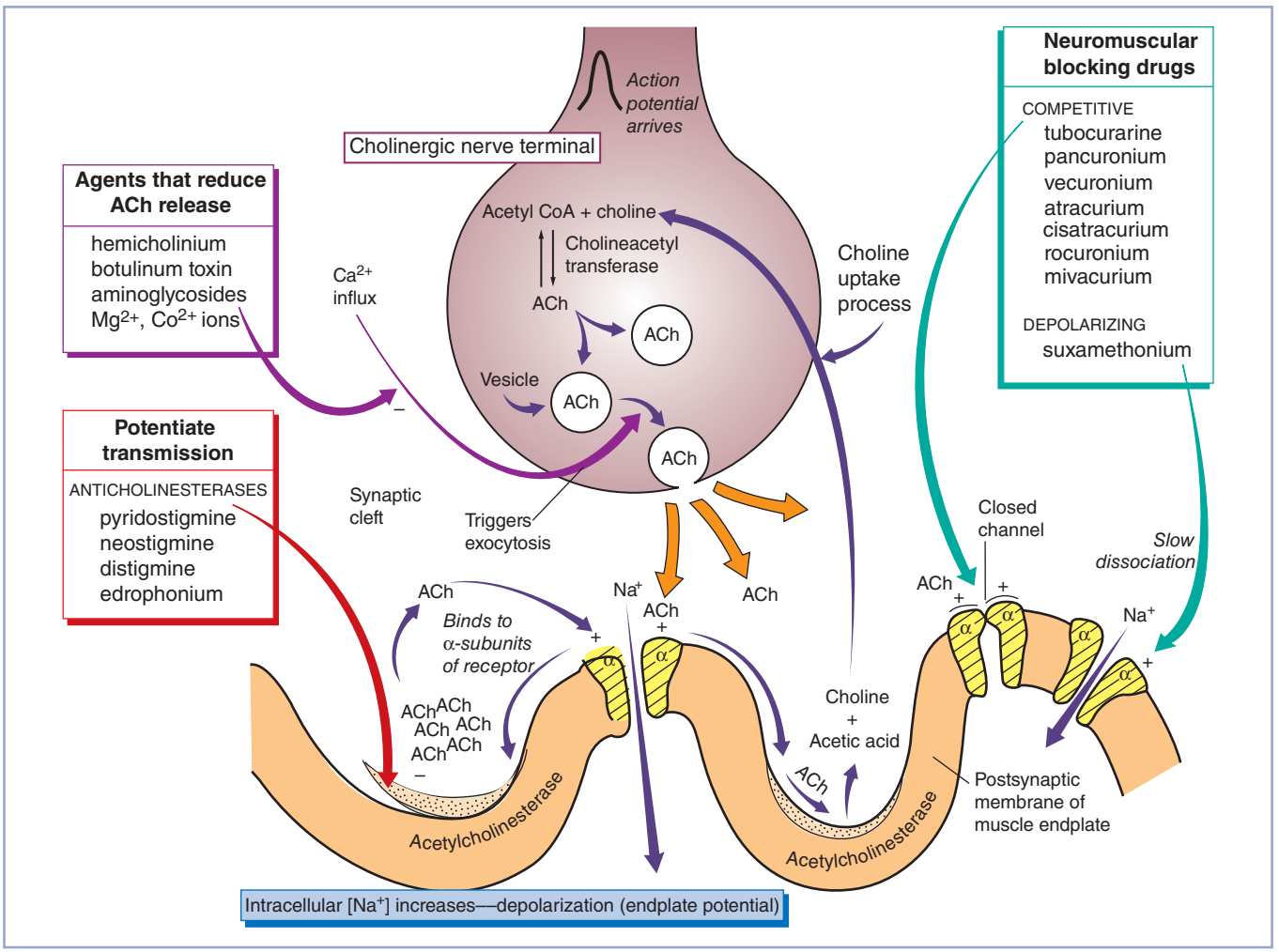
6 Drugs acting at the neuromuscular junction



Action potentials are conducted along the motor nerves to their terminals (upper figure, ▭) where the depolarization initiates an influx of Ca^{2+} ions and the release of **acetylcholine** (ACh) by a process of **exocytosis** (⇨). The acetylcholine diffuses across the junctional cleft and binds to receptors located on the surface of the muscle fibre membrane at the motor endplate. The reversible combination of acetylcholine and receptors (lower figure, ▨) triggers the opening of cation-selective channels in the endplate membrane, allowing an influx of Na^+ ions and a lesser efflux of K^+ ions. The resulting depolarization, which is called an endplate potential (EPP), depolarizes the adjacent muscle fibre membrane. If large enough, this depolarization results in an action potential and muscle contraction. The acetylcholine released into the synaptic cleft is rapidly hydrolysed by an enzyme, acetylcholinesterase (▩), which is present in the endplate membrane close to the receptors.

Neuromuscular transmission can be increased by **anticholinesterase drugs** (bottom left), which inhibit acetylcholinesterase and slow down the hydrolysis of acetylcholine in the synaptic cleft (see also Chapter 8). *Neostigmine* and *pyridostigmine* are used in the treatment of **myasthenia gravis** and to reverse competitive neuromuscular blockade after surgery. Overdosage of anticholinesterase results in excess acetylcholine and a depolarization block of motor endplates ('cholinergic crisis'). The muscarinic effects of acetylcholine (see Chapter 7) are also potentiated by anticholinesterases, but are blocked with atropine. Edrophonium has a very short action and is only used to diagnose myasthenia gravis.

Neuromuscular blocking drugs (right) are used by anaesthetists to relax skeletal muscles during surgical operations and to prevent muscle contractions during electroconvulsive therapy (ECT). Most of the clinically useful neuromuscular blocking drugs compete with acetylcholine for the receptor but do not initiate ion channel opening. These **competitive antagonists** reduce the endplate depolarizations produced by acetylcholine to a size that is below the threshold for muscle action potential generation and so cause a flaccid paralysis. **Depolarizing blockers** also act on acetylcholine receptors, but trigger the opening of the ion channels. They are not reversed by anticholinesterases. **Suxamethonium** is the only drug of this type used clinically.

Some agents (top left) act presynaptically and block neuromuscular transmission by preventing the release of acetylcholine.

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Acetylcholine

Acetylcholine is synthesized in motor neurone terminals from choline and acetyl coenzyme-A by the enzyme choline acetyltransferase. The choline is taken up into the nerve endings from the extracellular fluid by a special choline carrier located in the terminal membrane.

Exocytosis

Acetylcholine is stored in nerve terminals in the cytoplasm and within synaptic vesicles. When an action potential invades the terminal, Ca^{2+} ions enter and bind to synaptotagin on the vesicle membrane. This results in the association of a second vesicle-bound protein, synaptobrevin, with a protein on the inner surface of the plasma membrane. This association results in fusion with the presynaptic membrane. Several hundred 'packets' or 'quanta' of acetylcholine are released in about a millisecond. This is called quantal release and is very sensitive to the extracellular Ca^{2+} ion concentration. Divalent ions, such as Mg^{2+}, antagonize Ca^{2+} influx and inhibit transmitter release.

Acetylcholine receptor

This can be activated by nicotine and, for this reason, is called a **nicotinic receptor**.* The receptor–channel complex is pentameric and is constructed from four different protein subunits (ααβγε in the adult) that span the membrane and are arranged to form a central pore (channel) through which cations (mainly Na^+) flow. Acetylcholine molecules bind to the two α-subunits, inducing a conformational change that opens the channel for about 1 ms.

Myasthenia gravis

Myasthenia gravis is an autoimmune disease in which neuromuscular transmission is defective. Circulating heterogeneous immunoglobulin G (IgG) antibodies cause a loss of functional acetylcholine receptors in skeletal muscle. Syptomatic relief to counter the loss of receptors is obtained by the use of an **anticholinesterase**, usually pyridostigmine. Immunological treatment includes the administration of **prednisolone** or **azathioprine** (Chapter 45). Plasmapheresis, in which blood is removed and the cells returned, may improve motor function, presumably by reducing the level of immune complexes. Thymectomy may be curative.

Presynaptic agents

Drugs inhibiting acetylcholine release

Botulinum toxin is produced by *Clostridium botulinum* (an anaerobic bacillus, see Chapter 37). The exotoxin is extraordinarily potent and prevents acetylcholine release by enzymatically cleaving the proteins (e.g. synaptobrevin) required for docking of vesicles within the presynaptic membrane. *C. botulinum* is very rarely responsible for serious food poisoning in which the victims exhibit progressive parasympathetic and motor paralysis. **Botulinum toxin type A** is used in the treatment of certain dystonias, such as blepharospasm (spasmodic eye closure) and hemifacial spasm. In these conditions, low doses of toxin are injected into the appropriate muscle to produce paralysis that persists for about 12 weeks. In the USA botulinum toxin is used to treat urinary incontinence in patients with spinal cord injury and MS. Injected directly into the bladder, the toxin increases storage capacity and decreases incontinence.

*Pentameric nicotinic receptors also occur in autonomic ganglia and the brain. They have variants of the α- and β-subunit and a different pharmacology.

Aminoglycoside antibiotics (e.g. gentamicin) may cause neuromuscular blockade by inhibiting the calcium influx required for exocytosis. This unwanted effect usually occurs only as the result of an interaction with neuromuscular blockers. Myasthenia gravis may be exacerbated.

Competitive neuromuscular blocking drugs

In general, the competitive neuromuscular blocking drugs are bulky, rigid molecules and most have two quaternary N atoms. Neuromuscular blocking drugs are given by intravenous injection and are distributed in the extracellular fluid. They do not pass the blood–brain barrier or the placenta. The choice of a particular drug is often determined by the side-effects produced. These include histamine release, vagal blockade, ganglion blockade and sympathomimetic actions. The onset of action and the duration of action of neuromuscular blocking drugs depend on the dose, but also on other factors (e.g. prior use of suxamethonium, anaesthetic agent used).

Pancuronium is an aminosteroid neuromuscular blocking drug with a relatively long duration of action. It does not block ganglia or cause histamine release. However, it has a dose-related atropine-like effect on the heart that can produce tachycardia.

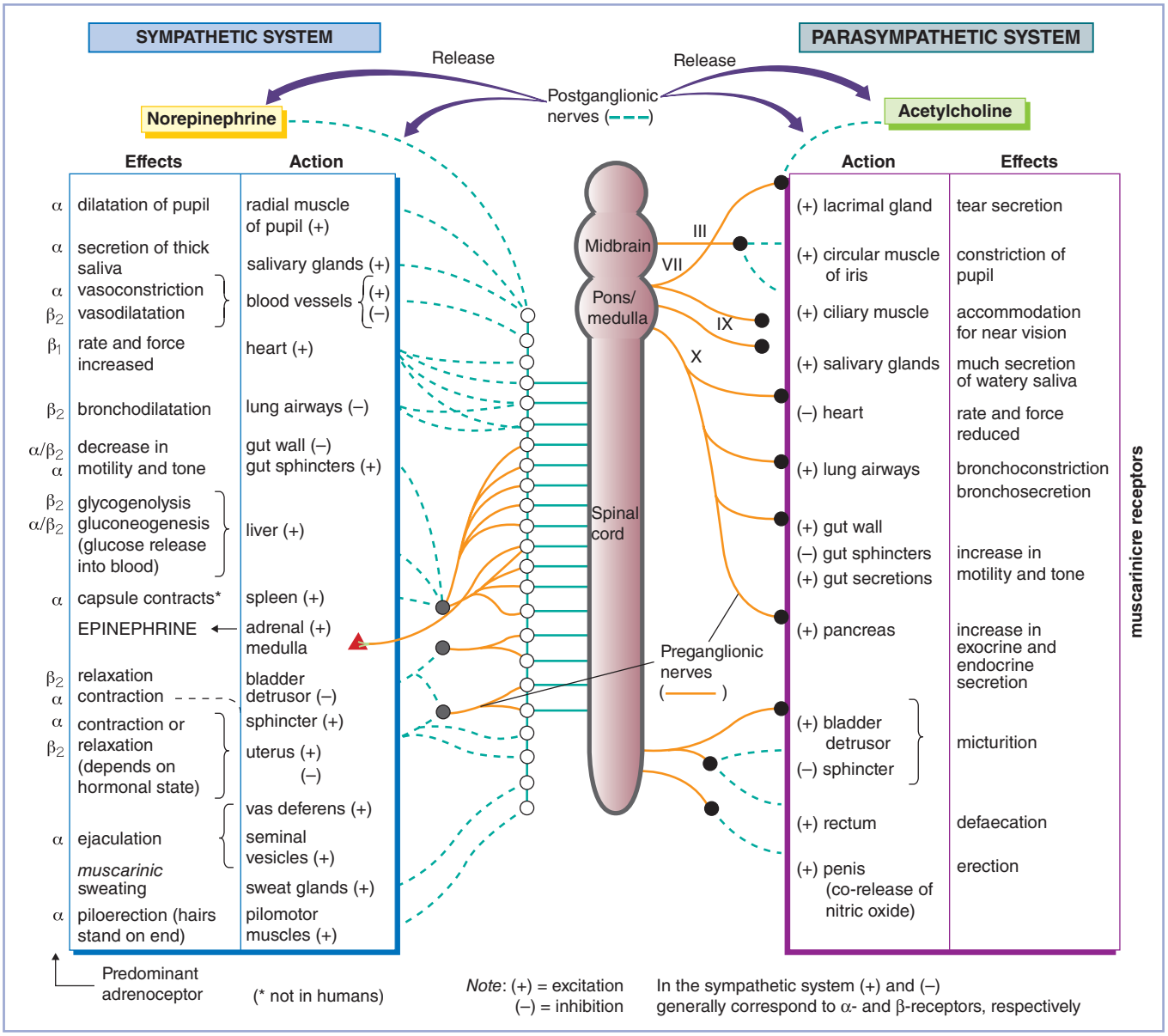
Vecuronium and atracurium are commonly used agents. **Vecuronium** has no cardiovascular effects. It depends on hepatic inactivation and recovery can occur within 20–30 min, making it an attractive drug for short procedures. **Atracurium** has a duration of action of 15–30 min. It is only stable when kept cold and at low pH. At body pH and temperature, it decomposes spontaneously in plasma and therefore does not depend on renal or hepatic function for its elimination. It is the drug of choice in patients with severe renal or hepatic disease. Atracurium may cause histamine release with flushing and hypotension. **Cisatracurium** is an isomer of atracurium. Its main advantage is that it does not cause histamine release and its associated cardiovascular effects.

Rocuronium has an intermediate duration of action of about 30 min, but with a rapid onset of action (1–2 min) comparable with that of suxamethonium (1–1.5 min). It has minimal cardiovascular effects.

Depolarizing neuromuscular blocking drugs

Suxamethonium (succinylcholine) is used because of its rapid onset and very short duration of action (2–6 min). The drug is normally hydrolysed rapidly by plasma pseudocholinesterase, but a few people (about 1 in 3000) inherit an atypical form of the enzyme and, in such individuals, the neuromuscular block may last for hours. Suxamethonium depolarizes the endplate and, because the drug does not dissociate rapidly from the receptors, a prolonged receptor activation is produced. The resulting endplate depolarization initially causes a brief train of muscle action potentials and muscle fibre twitches. Neuromuscular block then occurs as a result of several factors which include: (i) inactivation of the voltage-sensitive Na^+ channels in the surrounding muscle fibre membrane, so that action potentials are no longer generated; and (ii) transformation of the activated receptors to a 'desensitized' state, unresponsive to acetylcholine. The main disadvantage of suxamethonium is that the initial asynchronous muscle fibre twitches cause damage, which often results in muscle pains the next day. The damage also causes potassium release. Repeated doses of suxamethonium may cause bradycardia in the absence of atropine (a muscarinic effect).

7 Autonomic nervous system



Many systems of the body (e.g. digestion, circulation) are controlled automatically by the autonomic nervous system (and the endocrine system). Control of the autonomic nervous system often involves negative feedback, and there are many afferent (sensory) fibres that carry information to centres in the hypothalamus and medulla. These centres control the outflow of the autonomic nervous system, which is divided on anatomical grounds into two major parts: the **sympathetic system** (left) and the **parasympathetic system** (right). Many organs are innervated by both systems, which in general have opposing actions. The actions of sympathetic (left) and parasympathetic (right) stimulation on different tissues are indicated in the inner columns, and the resulting effects on different organs are shown in the outer columns.

The sympathetic nerves (left, ——) leave the thoracolumbar region of the spinal cord (T1–L3) and synapse either in the **paravertebral ganglia** (◯) or in the **prevertebral ganglia** (●) and plexuses in the abdominal cavity. Postganglionic non-myelinated nerve fibres (left, – – –) arising from neurones in the ganglia innervate most organs of the body (left).

The transmitter substance released at sympathetic nerve endings is noradrenaline (**norepinephrine**; top left). Inactivation of this transmitter occurs largely by reuptake into the nerve terminals. Some preganglionic sympathetic fibres pass directly to the adrenal medulla (▲), which can release adrenaline (**epinephrine**) into the circulation. Norepinephrine and epinephrine produce their actions on effector organs by acting on α-, β_1- or β_2-**adrenoceptors** (extreme left).

In the parasympathetic system, the preganglionic fibres (right, ——) leave the central nervous system via the cranial nerves (especially III, VII, IX and X) and the third and fourth sacral spinal

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roots. They often travel much further than sympathetic fibres before synapsing in ganglia (●), which are often in the tissue itself (right).

The nerve endings of the postganglionic parasympathetic fibres (right, - - -) release **acetylcholine** (top right), which produces its actions on the effector organs (right) by activating muscarinic receptors. Acetylcholine released at synapses is inactivated by the enzyme acetylcholinesterase.

All the preganglionic nerve fibres (sympathetic and parasympathetic, ——) are myelinated and release acetylcholine from the nerve terminals; the acetylcholine depolarizes the ganglionic neurones by activating nicotinic receptors.

A small proportion of autonomic nerves release neither acetylcholine nor norepinephrine. For example, the cavernous nerves release nitric oxide (NO) in the penis. This relaxes the smooth muscle of the corpora cavernosa (via cyclic guanosine monophosphate [cGMP], Chapter 16) allowing expansion of the lacunar spaces and erection. **Sildenafil**, used in male sexual dysfunction, inhibits phosphodiesterase type 5 and, by increasing the concentration of cGMP, facilitates erection.

Adrenaline mimics most sympathetic effects, i.e. it is a *sympatho-mimetic agent* (Chapter 9). Elliot suggested in 1904 that adrenaline was the sympathetic transmitter substance, but Dale pointed out in 1910 that **noradrenaline** mimicked sympathetic nerve stimulation more closely.

Effects of sympathetic stimulation

These are most easily remembered by thinking of changes in the body that are appropriate in the '*fight or flight reaction*'. Note which of the following effects are excitatory and which are inhibitory.

1 Pupillary dilatation (more light reaches the retina).
2 Bronchiolar dilatation (facilitates increased ventilation).
3 Heart rate and force are increased; blood pressure rises (more blood for increased activity of skeletal muscles – running!).
4 Vasoconstriction in skin and viscera and vasodilatation in skeletal muscles (appropriate redistribution of blood to muscles).
5 To provide extra energy, glycogenolysis is stimulated and the blood glucose level increases. The gastrointestinal tract and urinary bladder relax.

Adrenoceptors

These are divided into two main types: *α-receptors* mediate the excitatory effects of sympathomimetic amines, whereas their inhibitory effects are generally mediated by *β-receptors* (exceptions are the smooth muscle of the gut, for which α-stimulation is inhibitory, and the heart, for which β-stimulation is excitatory). Responses mediated by α- and β-receptors can be distinguished by: (i) phentolamine and propranolol, which *selectively* block α- and β-receptors, respectively; and (ii) the relative potencies, on different tissues, of norepinephrine (NE), epinephrine (E) and isoprenaline (I). The order of potency is NE > E > I where excitatory (α) responses are examined, but for inhibitory (β) responses this order is reversed (I >> E > NE).

β-Adrenoceptors are not homogeneous. For example, norepinephrine is an effective stimulant of cardiac β-receptors, but has little or no action on the β-receptors mediating vasodilatation. On the basis of the type of differential sensitivity they exhibit to drugs, β-receptors are divided into two types: β_1 (heart, intestinal smooth muscle) and β_2 (bronchial, vascular and uterine smooth muscle).

α-Adrenoceptors are divided into two classes, originally depending on whether their location is postsynaptic (α_1) or presynaptic (α_2). Stimulation of the presynaptic α_2-receptors by synaptically released norepinephrine reduces further transmitter release (negative feedback). Postsynaptic α_2-receptors occur in a few tissues, e.g. brain, vascular smooth muscle (but mainly α_1).

Acetylcholine

Acetylcholine is the transmitter substance released by the following:

1 All preganglionic autonomic nerves (i.e. both sympathetic and parasympathetic).
2 Postganglionic parasympathetic nerves.
3 Some postganglionic sympathetic nerves (i.e. thermoregulatory sweat glands and skeletal muscle vasodilator fibres).
4 Nerve to the adrenal medulla.
5 Somatic motor nerves to skeletal muscle endplates (Chapter 6).
6 Some neurones in the central nervous system (Chapter 22).

Acetylcholine receptors (cholinoceptors)

These are divided into nicotinic and muscarinic subtypes (originally determined by measuring the sensitivity of various tissues to the drugs nicotine and muscarine, respectively).

Muscarinic receptors

Acetylcholine released at the nerve terminals of postganglionic parasympathetic fibres acts on muscarinic receptors and can be blocked selectively by atropine. Five subtypes of muscarinic receptor exist, three of which have been well characterized: M_1, M_2 and M_3. M_1-receptors occur in the brain and gastric parietal cells, M_2-receptors in the heart and M_3-receptors in smooth muscle and glands. Except for **pirenzepine**, which selectively blocks M_1-receptors (Chapter 12), clinically useful muscarinic agonists and antagonists show little or no selectivity for the different subtypes of muscarinic receptor.

Nicotinic receptors

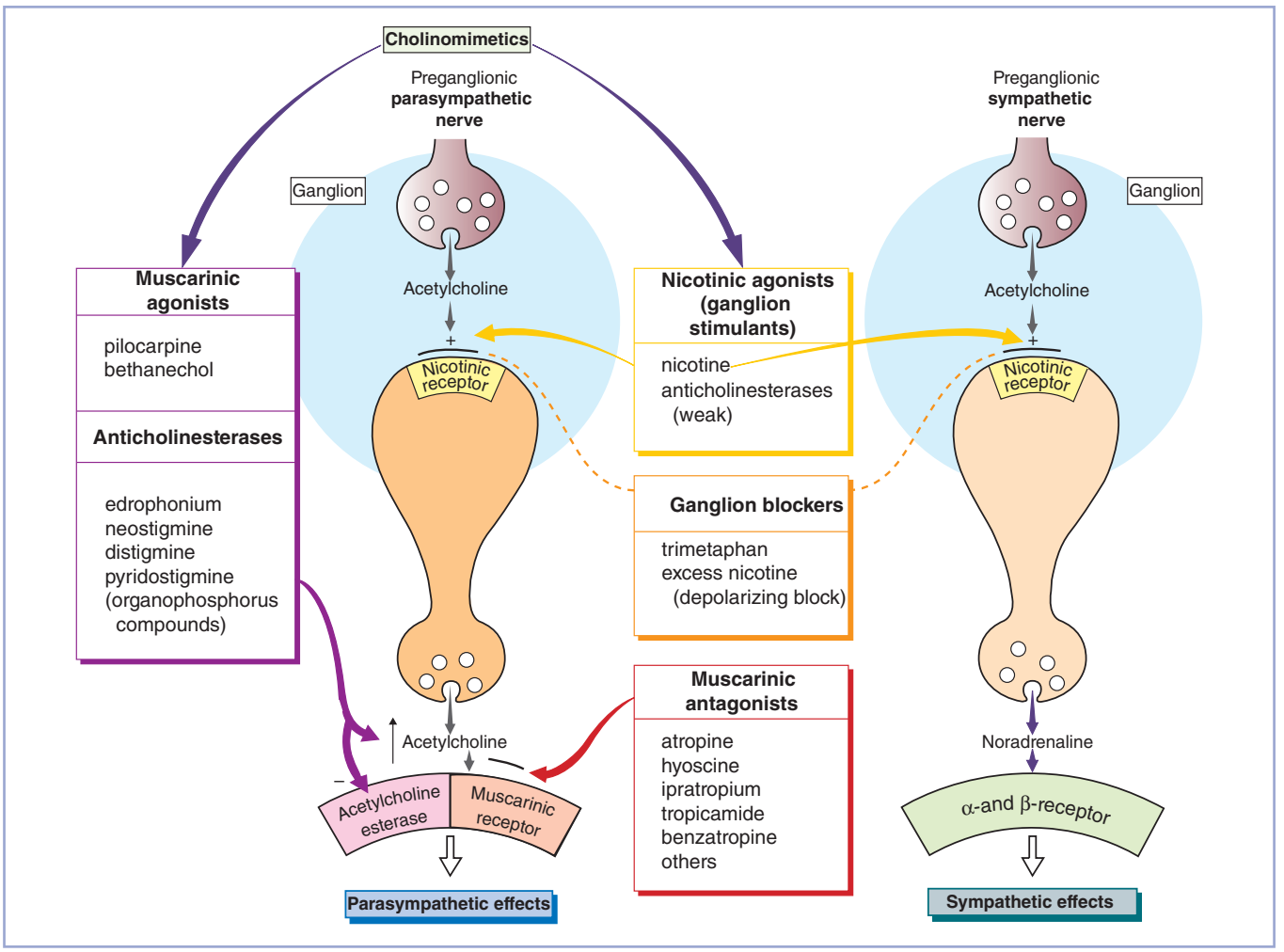
These occur in autonomic ganglia and in the adrenal medulla, where the effects of acetylcholine (or nicotine) can be blocked selectively with hexamethonium. The nicotinic receptors at the skeletal muscle neuromuscular junction are not blocked by hexamethonium, but are blocked by tubocurarine. Thus, receptors at ganglia and neuromuscular junctions are different, although both types are stimulated by nicotine and therefore called nicotinic.

Actions of acetylcholine

Muscarinic effects are mainly parasympathomimetic (except sweating and vasodilatation), and in general are the opposite of those caused by sympathetic stimulation. Muscarinic effects include: constriction of the pupil, accommodation for near vision (Chapter 10), profuse watery salivation, bronchiolar constriction, bronchosecretion, hypotension (as a result of bradycardia and vasodilatation), an increase in gastro-intestinal motility and secretion, contraction of the urinary bladder and sweating.

Nicotinic effects include stimulation of all autonomic ganglia. However, the action of acetylcholine on ganglia is relatively weak compared with its effect on muscarinic receptors, and so parasympathetic effects predominate. The nicotinic actions of acetylcholine on the sympathetic system can be demonstrated, for example, on cat blood pressure, by blocking its muscarinic actions with atropine. High intravenous doses of acetylcholine then cause a rise in blood pressure, because stimulation of the sympathetic ganglia and adrenal medulla now results in vasoconstriction and tachycardia.

8 Autonomic drugs acting at cholinergic synapses



Acetylcholine released from the terminals of postganglionic parasympathetic nerves (left, ▭) produces its actions on various effector organs by activating **muscarinic receptors** (▭). The effects of acetylcholine are usually excitatory, but an important exception is the heart, which receives inhibitory cholinergic fibres from the vagus (Chapter 17). Drugs that mimic the effects of acetylcholine are called **cholinomimetics** and can be divided into two groups:

- drugs that act directly on receptors (**nicotinic** and **muscarinic agonists**); and
- **anticholinesterases**, which inhibit acetylcholinesterase and so act indirectly by allowing acetylcholine to accumulate in the synapse and produce its effects.

Muscarinic agonists (top left) have few uses, but **pilocarpine** (as eyedrops) is sometimes used to reduce intraocular pressure in patients with glaucoma (Chapter 10). **Bethanechol** was used to stimulate the bladder in urinary retention, but it has been superseded by catheterization.

Anticholinesterases (bottom left) have relatively little effect at ganglia and are used mainly for their nicotinic effects on the neuromuscular junction. They are used in the treatment of myasthenia gravis and to reverse the effects of competitive muscle relaxants used during surgery (Chapter 6).

Muscarinic antagonists (bottom middle) block the effects of acetylcholine released from postganglionic parasympathetic nerve terminals. Their effects can, in general, be worked out by examination of the figure in Chapter 7. However, parasympathetic effector organs vary in their sensitivity to the blocking effect of antagonists. Secretions of the salivary, bronchial and sweat glands are most sensitive to blockade. Higher doses of antagonist dilate the pupils, paralyze accommodation and produce tachycardia by blocking vagal tone in the heart. Still higher doses inhibit parasympathetic control of the gastrointestinal tract and bladder. Gastric acid secretion is most resistant to blockade (Chapter 12).

Atropine, **hyoscine** (scopolamine) or other antagonists are used:

1 in anaesthesia to block vagal slowing of the heart and to inhibit bronchial secretion;
2 to reduce intestinal spasm in, for example, irritable bowel syndrome (Chapter 13);

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3 in Parkinson's disease (e.g. benzatropine, Chapter 26);
4 to prevent motion sickness (hyoscine, Chapter 30);
5 to dilate the pupil for ophthalmological examination (e.g. tropicamide) or to paralyse the ciliary muscle (Chapter 10);
6 as a bronchodilator in asthma (ipratropium, Chapter 11) and
7 in urinary incontinence antimuscarinic drugs e.g. solfenacin, darifenacin reduce detrusor muscle overactivity.

Transmission at autonomic ganglia ( ) can be stimulated by nicotinic agonists (top middle) or blocked by drugs that act specifically on the ganglionic neurone nicotinic receptor/ionophore (middle). Nicotinic agonists are of no clinical use and ganglion blocking drugs, e.g. hexamethonium, are only of historical interest.

Cholinergic nerve terminals in the autonomic nervous system synthesize, store and release acetylcholine in essentially the same way as at the neuromuscular junction (Chapter 6). Acetylcholinesterase is bound to both the pre- and postsynaptic membranes.

Cholinomimetics

Muscarinic agonists

These directly activate muscarinic receptors, usually producing excitatory effects. An important exception is the heart, where activation of the predominantly M_2-receptors has inhibitory effects on the rate and force of (atrial) contraction. The M_2-receptors are negatively coupled by a G-protein (G_1) to adenylyl cyclase, which explains the negative inotropic effect of acetylcholine. Subunits ($\beta\gamma$)) of G_1 directly increase K^+ conductances in the heart causing hyperpolarization and bradycardia (Chapter 17). Acetylcholine stimulates glandular secretion and causes contraction of smooth muscle by activating M_3-receptors, which are coupled to the formation of inositol-1,4,5-trisphosphate ($InsP_3$) and diacylglycerol (Chapter 1). $InsP_3$ increases cytosolic Ca^{2+}, thus triggering muscle contraction or glandular secretion. An intravenous injection of acetylcholine causes vasodilatation indirectly by releasing nitric oxide (NO) from vascular endothelial cells (Chapter 16). However, most blood vessels have no parasympathetic innervation and so the physiological function of vascular muscarinic receptors is uncertain.

Choline esters

Bethanechol is a quaternary compound that does not penetrate the blood–brain barrier. Its actions are much more prolonged than those of acetylcholine, because it is not hydrolyzed by cholinesterase.

Pilocarpine possesses a tertiary N atom, which confers increased lipid solubility. This enables the drug to penetrate the cornea readily when applied locally, and enter the brain when given systemically.

Anticholinesterases

These are indirectly acting cholinomimetics. The commonly used anticholinesterase drugs are quaternary compounds that do not pass the blood–brain barrier and have negligible central effects. They are poorly absorbed orally. **Physostigmine** (eserine) is much more lipid soluble. It is well absorbed after oral or local administration (e.g. as eyedrops) and passes into the brain.

Mechanism of action

Initially, acetylcholine binds to the active site of the esterase and is hydrolyzed, producing free choline and acetylated enzyme. In a second step, the covalent acetyl–enzyme bond is split with the addition of water. **Edrophonium** is the main example of a reversible anticholinesterase. It binds by electrostatic forces to the active site of the enzyme. It does not form covalent bonds with the enzyme and so is very short acting (2–10 min). The carbamate esters (e.g. **neostigmine**, **pyridostigmine**) undergo the same two-step process as acetylcholine, except that the breakdown of the carbamylated enzyme is much slower (30 min to 6 h). Organophosphorus agents result in a phosphorylated enzyme active site. The covalent phosphorus–enzyme bond is very stable and the enzyme is inactivated for hundreds of hours. For this reason, the organophosphorus compounds are referred to as irreversible anticholinesterases. They are extremely toxic and are used as insecticides (parathion, malathion) and chemical warfare agents (e.g. sarin). Malathion is used topically in the treatment of scabies and head lice.

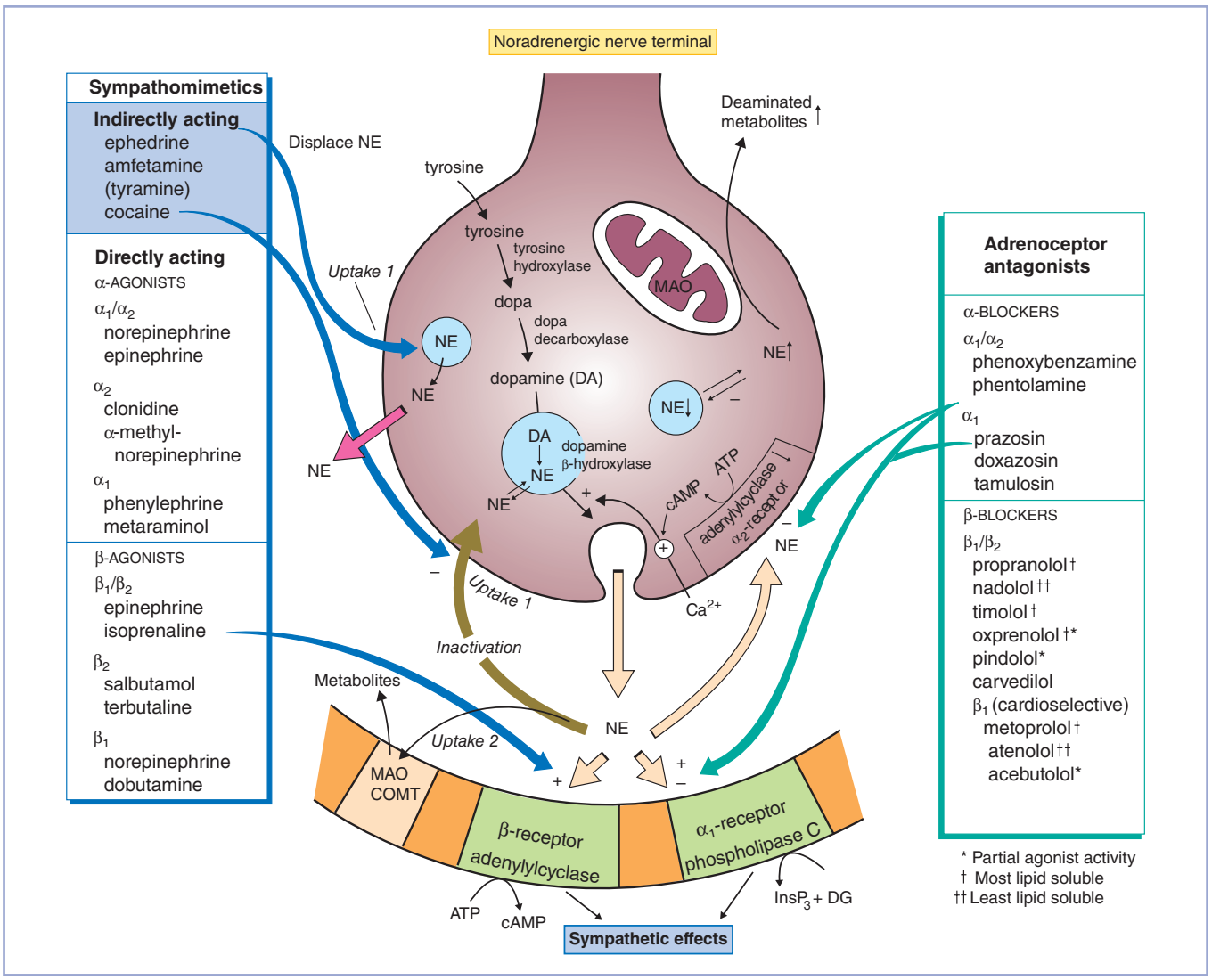
The effects of anticholinesterases are generally similar to those produced by the directly acting muscarinic agonists, but, in addition, transmission at the neuromuscular junction is potentiated. The cholinesterase inhibitors produce less vasodilatation than the directly acting agonists because they can only act on the (few) vessels possessing cholinergic innervation. Also, stimulation of sympathetic ganglia may oppose the vasodilator effects of the drug. Only large toxic doses of anticholinesterase produce marked bradycardia and hypotension.

Toxic doses initially cause signs of extreme muscarinic stimulation: miosis, salivation, sweating, bronchial constriction, bronchosecretion, vomiting and diarrhoea. Excessive stimulation of nicotinic receptors may cause depolarizing neuromuscular blockade. If the drug is lipid soluble (e.g. organophosphorus compounds, except ecothiopate), convulsions, coma and respiratory arrest may occur. Strong nucleophiles (e.g. **pralidoxime**) can split the phosphorus–enzyme bond initially formed by organophosphorus compounds and 'regenerate' the enzyme. Later, this becomes impossible because a process of 'ageing' strengthens the phosphorus–enzyme bond.

Muscarinic antagonists (antimuscarinics)

Atropine occurs in deadly nightshade (*Atropa belladonna*). It is a weak central stimulant, especially on the vagal nucleus, and low doses often cause bradycardia. Higher doses cause tachycardia. **Hyoscine** (*scopolamine*) is more sedative than atropine and often produces drowsiness and amnesia. Toxic doses of both drugs cause excitement, agitation, hallucination and coma. The effects of muscarinic antagonists can be worked out by studying the figure in Chapter 7. The student should understand why these drugs produce dilated pupils, blurred vision, dry mouth, constipation and difficulty with micturition. The latter effect, although usually unwanted, is useful in patients with overactive bladder associated with urinary incontinence. Antimuscarinic drugs (e.g. *solfenacin, darifenacin*) reduce detrusor muscle overactivity probably by an action on M_3-receptors.

9 Drugs acting on the sympathetic system



The sympathetic nervous system is important in regulating organs such as the heart and peripheral vasculature (Chapters 15 and 18). The transmitter released from sympathetic nerve endings is **norepinephrine** (**NE**) (noradrenaline, ⇨) but, in response to some forms of stress, **epinephrine** (adrenaline) is also released from the adrenal medulla. These catecholamines are inactivated mainly by **reuptake** (⇨).

Sympathomimetics (left) are drugs that partially or completely mimic the actions of norepinephrine and epinephrine. They act either directly on α- and/or β-adrenoceptors (left, open column) or **indirectly** on the presynaptic terminals (top left, shaded), usually by causing the release of norepinephrine (⇨). The effects of adrenoceptor stimulation can be seen in the figure in Chapter 7.

β_2-adrenoceptor agonists cause bronchial dilatation and are used in the treatment of asthma (Chapter 11). They are also used to relax uterine muscle in an attempt to prevent preterm labour. **β_1-adrenoceptor agonists** (dobutamine) are sometimes used to stimulate the force of heart contraction in severe low-output heart failure (Chapter 18). **α_1-agonists** (e.g. **phenylephrine**) are used as mydriatics (Chapter 10) and in many popular decongestant preparations. **α_2-agonists**, notably **clonidine** and **methyldopa** (which acts after its conversion to α-methylnorepinephrine, a false transmitter), are centrally acting hypotensive drugs (Chapter 15).

Sympathomimetic amines that act mainly by causing **norepinephrine release** (e.g. **amfetamine**) have the α_1/α_2 selectivity of norepinephrine. **Ephedrine**, in addition to causing norepinephrine release, also has a direct action. Its effects resemble those of epinephrine, but last much longer. Ephedrine is a mild central stimulant, but amfetamine, which enters the brain more readily, has a much greater stimulant effect on mood and alertness

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and a depressant effect on appetite. Amfetamine and similar drugs have a high abuse potential and are rarely used (Chapter 31).

β-adrenoceptor antagonists (**β-blockers**) (bottom right) are important drugs in the treatment of angina (Chapter 16), cardiac arrhythmias (Chapter 17), heart failure (Chapter 18) and glaucoma (Chapter 10). **α-adrenoceptor antagonists** (**α-blockers**) (middle right) have limited clinical applications. They are used in the treatment of benign prostatic hyperplasia (BPH), phaeochromocytoma and as a third-line drug in hypertension (Chapter 15).

Reuptake of norepinephrine by a high-affinity transport system (Uptake 1) in the nerve terminals 'recaptures' most of the transmitter and is the main method of terminating its effects. A similar (extraneuronal) transport system (Uptake 2) exists in the tissues but is less selective and less easily saturated.

Monoamine oxidase (**MAO**) and **catechol-O-methyltransferase** (**COMT**) are widely distributed enzymes that catabolize catecholamines. Inhibition of MAO and COMT has little potentiating effect on responses to sympathetic nerve stimulation or injected catecholamines (norepinephrine, epinephrine) because they are largely inactivated by reuptake.

α_1-adrenoceptors are postsynaptic. Their activation in several tissues (e.g. smooth muscle, salivary glands) causes an increase in inositol-1,4,5-trisphosphate and subsequently cytosolic calcium (Chapter 1), which triggers vasoconstriction or glandular secretion.

α_2-adrenoceptors occur on noradrenergic nerve terminals. Their activation by norepinephrine inhibits adenylyl cyclase. The consequent fall in cyclic adenosine monophosphate (cAMP) closes Ca^{2+} channels and diminishes further transmitter release.

β-adrenoceptor activation results in stimulation of adenylyl cyclase, increasing the conversion of adenosine triphosphate (ATP) to cAMP. The cAMP acts as a 'second messenger', coupling receptor activation to response.

Sympathomimetics

Indirectly acting sympathomimetics

Indirectly acting sympathomimetics resemble the structure of norepinephrine closely enough to be transported by Uptake 1 into nerve terminals where they displace vesicular norepinephrine into the cytoplasm. The norepinephrine is then transported out of the nerve terminal by the reverse action of uptake 1 and activates adrenoceptors.

Amfetamines are resistant to MAO. Their peripheral actions (e.g. tachycardia, hypertension) and central stimulant actions are mainly caused by catecholamine release. **Dexamfetamine** and **methylphenidate** are sometimes used in hyperkinetic children. Dexamfetamine and **modafinil** may be beneficial in narcolepsy. Dependence on amfetamine-like drugs is common (Chapter 31).

Cocaine, in addition to being a local anaesthetic (Chapter 5), is a sympathomimetic because it inhibits the reuptake of norepinephrine by nerve terminals. It has an intense central stimulant effect that has made it a popular drug of abuse (Chapter 31).

Directly acting sympathomimetics

The effect of sympathomimetic drugs in humans depends on their receptor specificity (α and/or β) and on the compensatory reflexes they evoke.

Epinephrine and **norepinephrine** are destroyed in the gut and are short lasting when injected because of uptake and metabolism. Epinephrine increases the blood pressure by stimulating the rate and force of the heartbeat (β_1-effects). Stimulation of vascular α-receptors causes vasoconstriction (viscera, skin), but β_2-stimulation causes vasodilatation (skeletal muscle) and the total peripheral resistance may actually decrease.

Norepinephrine has little or no effect on the vascular β_2-receptors, and so the α-mediated vasoconstriction is unopposed. The resulting rise in blood pressure reflexively slows the heart, usually overcoming the direct β_1-stimulant action on the heart rate.

Epinephrine by injection has an important use in the treatment of *anaphylactic shock* (Chapter 11).

β-receptor-selective drugs

Isoprenaline stimulates all β-receptors, increasing the rate and force of the heartbeat and causing vasodilatation. These effects result in a fall in diastolic and mean arterial pressure with little change in systolic pressure.

β_2-adrenoceptor agonists are relatively selective drugs that produce bronchodilatation at doses that cause minimal effects on the heart. They are resistant to MAO and are probably not taken up into neurones. Their main use is in the treatment of asthma (Chapter 11).

Adrenoceptor antagonists

α-blockers

α-blockers reduce arteriolar and venous tone, causing a fall in peripheral resistance and blood pressure (Chapter 15). α-blockers cause a reflex tachycardia, which is greater with non-selective drugs that also block α_2-presynaptic receptors on the heart, because the augmented release of norepinephrine stimulates further the cardiac β-receptors. **Prazosin**, a selective α_1-antagonist, causes relatively little tachycardia. **BPH** is common in men over 50 years old. As the prostate gland increases in size, pressure on the urethra obstructs urine flow. α_1-blockers increase urine flow (at least partially) by relaxing smooth muscle in the gland. **Tamsulosin** is selective for α_{1A}-adrenoceptors and is better tolerated than other antagonists.

β-blockers

β-blockers vary in their *lipid solubility* and *cardioselectivity*. However, they all block β_1-receptors and are equally effective in reducing blood pressure and preventing angina. The more lipid-soluble drugs are more rapidly absorbed from the gut, undergo more first-pass hepatic metabolism and are more rapidly eliminated. They are also more likely to enter the brain and cause central effects (e.g. bad dreams). *Cardioselectivity* is only relative and diminishes with higher doses. Nevertheless, selective β_1-blockade seems to produce less peripheral vasoconstriction (cold hands and feet) and does not reduce the response to exercise-induced hypoglycaemia (stimulation of gluconeogenesis in the liver is mediated by β_2-receptors). Cardioselective drugs may have sufficient β_2-activity to precipitate severe bronchospasm in patients with asthma and they should avoid β-blockers. Some β-blockers possess *intrinsic sympathomimetic activity* (i.e. are partial agonists, Chapter 2). The clinical importance of this is debatable, see Chapter 16.