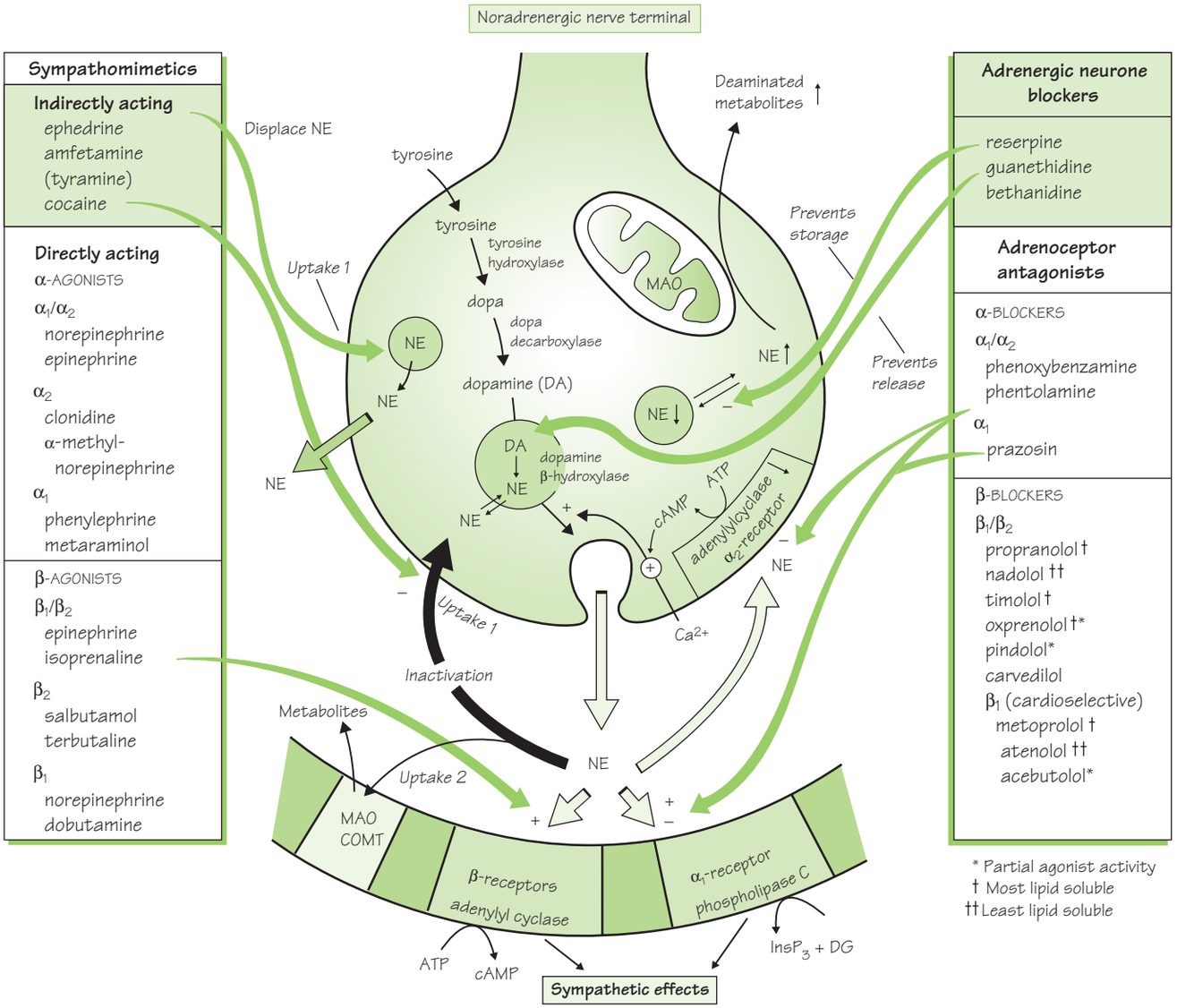
9 Drugs acting on the sympathetic system



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 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 hypertension (Chapter 15), 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. **Prazosin**, a selective α_1-antagonist, is sometimes used in the treatment of hypertension. **Phenoxybenzamine**, an irreversible antagonist, is used to block the α-effects of the large amounts of catecholamines released from tumours of the adrenal medulla (phaeochromocytoma). Many α-blockers have been (and are) used in the treatment of peripheral vascular occlusive disease, usually with little success.

Adrenergic neurone-blocking drugs (top right, shaded) either deplete the nerve terminals of norepinephrine (reserpine) or prevent its release. They were used as hypotensive agents (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. Some of the norepinephrine is metabolized by MAO, but the remainder is released by carrier-mediated transport to activate 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 heart beat (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 heart beat 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 hypotension (Chapter 15). They reverse the pressor effects of epinephrine, because its β_2-mediated vasodilator effects are unopposed by α-mediated vasoconstriction and the peripheral resistance falls (epinephrine reversal). 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.

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, but see Chapter 16.