Drugs affecting the autonomic nervous system

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Abstract

The autonomic nervous system (ANS) is a complex system of nervous and humoral mechanisms that modulates the function of the autonomous or visceral organs. Autonomic control of organs aims to maintain homoeostasis in health. Many drugs used in clinical practice can have either primary or secondary effects on the function of autonomic nervous system.

Keywords Autonomic nervous system; catecholamines; parasympathetic; sympathetic

Royal College of Anaesthetists CPD Matrix: 1A02, 2C04.

Learning objectives

After reading this article, you should be able to:

- identify five sympathomimetic drugs, their indications and doses
- identify five sympatholytic drugs, their indications and doses
- explain the biosynthesis of endogenous catecholamines

The autonomic nervous system (ANS) is divided on anatomical, physiological and pharmacological grounds into sympathetic (SNS) and parasympathetic (PNS) nervous systems (Tables 1 and 2). Both the SNS and PNS consist of pre- and post-ganglionic neurones. Pre-ganglionic fibres of the SNS arise from the thoracolumbar regions of the spinal cord, with pre-ganglionic fibres of the PNS arising from the craniosacral regions. Pre-ganglionic transmission in both the SNS and PNS is mediated via acetylcholine (ACh), acting at nicotinic acetylcholine receptors.

Post-ganglionic transmission in SNS neurones is primarily mediated by noradrenaline, acting via specific adrenergic receptors, except in sweat glands and the adrenal gland. Sweat gland post-ganglionic neurones release ACh. Pre-ganglionic fibres of the adrenal gland synapse directly with the adrenal medulla, stimulating the release of adrenaline from enterochromaffin cells. Adrenergic receptors are classified into three major types (α_1, α_2, and β), with further subtypes in each class. Two subtypes of β-receptor (β_1 and β_2) are well defined on functional, anatomical and pharmacological grounds and a third β-receptor subtype, β_3, is found in adipocytes, skeletal and ventricular muscle, and the vasculature. Dopaminergic (DA) receptors are now classified separately from adrenoceptors but are included here due to overlap in their actions and response to exogenous and endogenous catecholamines. There are five subtypes of DA receptors (D_1—D_5) belonging to two subfamilies: D_1-like and D_2-like. D_1-like receptors mediate vasodilatation in vascular smooth muscle of the renal, splanchnic, coronary and cerebral circulations; D_2-like receptors are widespread in the central nervous system.

Post-ganglionic transmission in the PNS is mediated via acetylcholine, acting via muscarinic acetylcholine receptors of which there are five subtypes (M_{1-5}).

Post-ganglionic muscarinic and adrenergic receptors are coupled to membrane-bound G-proteins and elicit a response through second and third messenger systems that vary with receptor subtype (Table 1).

Termination of neurotransmitter activity is brought about by a number of mechanisms. Acetylcholine is rapidly hydrolysed by the enzyme acetylcholinesterase to acetate and choline. Noradrenaline is removed from the synaptic junction by the *reuptake* system, being returned to the sympathetic nerve that released it. It is subsequently metabolized intra-neuronally by monoamine oxidase (MAO) enzymes. Circulating catecholamines and metabolized by the catechol-O-methyltransferase (COMT) enzyme system in the liver.[1]

Drugs acting on the sympathetic nervous system

Drugs with effects that mimic stimulation of SNS or adrenal medullary discharge are termed sympathomimetics; drugs that antagonize the sympathetic nervous system effects are called sympatholytics. Other more recent methods of modulating the autonomic nervous system (such as implantable carotid sinus stimulators or renal nerve ablation procedures) have been introduced for the treatment of drug-resistant hypertension; these are outside the scope of this article.

Sympathomimetics

Sympathomimetics mimic SNS stimulation by one of three mechanisms, acting directly on adrenoceptors (e.g. catecholamines, phenylephrine and methoxamine), indirectly by stimulating release of noradrenaline from nerve endings (e.g. amphetamine), or by combination of both mechanisms (e.g. dopamine, ephedrine and metaraminol). Sympathomimetics can be classified pharmacologically according to their structure (catecholamine/non-catecholamine); origin (endogenous/synthetic) and site of action (adrenoceptor/non-adrenoceptor).

Catecholamines

Catecholamine drugs can be endogenous or synthetic. All catecholamines are based on a benzene ring structure with hydroxyl

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Adrenoceptors and acetylcholine receptors

Adrenoceptors				Acetylcholine receptors			
Receptor	**Location**	**Second messenger**	**Selective antagonist e.g.**	**Receptor**	**Location**	**Second messenger**	**Selective antagonist e.g.**
α_1	Smooth muscle, skeletal muscle, cardiac muscle, Liver	IP_3 (G_q)	Prazosin, Doxazosin, Indoramin	*Muscarinic* M_1	CNS, stomach, autonomic ganglia	IP_3	Pirenzepine
α_2	Presynaptic sympathetic nerves, CNS, platelets	↓ cAMP (G_i)	Yohimbine, Idazoxan	M_2	Heart, CNS, autonomic nerve endings	↓ cAMP (G_i)	None
β_1	Heart	cAMP (G_s)	Atenolol, Metoprolol, Bisoprolol, Esmolol	M_3	CNS, salivary and mucous glands	IP_3	None
β_2	Smooth muscle, skeletal muscle, cardiac muscle, liver	cAMP (G_s)		M_4	CNS, cardiac muscle	↓ cAMP (G_i)	None
β_3	Fat, subcutaneous tissue	cAMP (G_s)		M_5	?CNS	IP_3	None
Nicotinic N_1 (muscle receptors)					Motor endplate	Ion channel ↑ Na^+, ↑ Ca^{++} entry	
N_2 (neuronal receptors)					Autonomic ganglia	Ion channel ↑ Na^+, ↑ Ca^{++} entry	

Stimulation of β_{1-3} receptors results in the activation of GTP binding G_s proteins, which in turn activates adenylate cyclase enzymes, generating cAMP to mediate the associated altered cell function. Stimulated α_2, M_2 and M_4 receptors interact with G_i proteins to inhibit adenylate cyclase and hence reduce cAMP. Stimulation of α_1, M_1 and M_3 receptors causes an interaction with the G_q protein. This leads to activation of membrane-bound phospholipase C, hydrolysing phosphatidylinositol biphosphate (PIP_2) to Inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 binds to its receptor, opening Ca^{2+} channels. Nicotinic receptors are associated with non-selective ion channels that open up on their activation to effect changes.

Table 1

groups at the C3 and C4 positions. Substitutions in the amine side-chain lead to the different hormones. Catecholamines have very short half-lives *in vivo* and are immediately inactivated in the gut by monoamine oxidase (MAO) enzymes. They are therefore usually administered parenterally, with doses being titrated to clinical effect. Choice of catecholamine depends on the clinical indication, desired therapeutic response and duration of action.

Endogenous catecholamines

The endogenous catecholamines (dopamine, noradrenaline and adrenaline) are synthesized from the essential amino acid phenylalanine (Figure 1).

Adrenaline (epinephrine) is the principle catecholamine (80–90%) synthesized by the adrenal medulla and is a potent, non-selective sympathomimetic. It can administered intravenously (IV), intramuscularly (IM), topically or via nebulizer or tracheal tube. In non-emergency situations, adrenaline should be administered IM to reduce the risk of cardiac arrhythmias and intense vasoconstriction. In emergency situations (e.g. cardiac arrest, peri-arrest and anaphylaxis) the IV route is indicated.

The effects of adrenaline are dose-dependent. In low doses, β-effects predominate, leading to bronchodilation, and an increase in heart rate, cardiac output and myocardial oxygen consumption. Vasodilatation of skeletal muscle and splanchnic arterioles leads to a decrease in peripheral vascular resistance seen clinically as reduced diastolic pressure. At higher infusion rates or bolus doses, α_1-effects predominate, with vasoconstriction leading to an increase in systemic vascular resistance.

Adrenaline is included in a number of algorithms supported by the Resuscitation Council (UK), including those for cardiac arrest and anaphylaxis.[2] In cardiac arrest scenarios, adrenaline is administered at a dose of 1 mg (10 ml of 1:10,000 [0.1 mg/ml]) at alternating CPR cycles, with commencement depending on presenting rhythm. In anaphylaxis adrenaline is usually administered IM at a dose of 500 mcg (0.5 of 1:1000 [1 mg/ml] solution), although IV doses of 50–100 μg (0.5–1 ml of 1:10,000 [0.1 mg/ml]) can alternatively be used. Adrenaline can be given by continuous infusion in shock states, administered at a dose range of 0.01–0.5 μg/kg/minute.

Adrenaline is incorporated into local anaesthetic solutions, prolonging their duration of action by decreasing systemic adsorption (due to localized vasoconstriction). Adrenaline is also used as a topical vasoconstrictor to achieve local haemostasis and in the treatment of wide-angle glaucoma.

Noradrenaline (norepinephrine) is synthesized in the adrenal medulla and post-ganglionic sympathetic nerve endings from the essential amino acid tyrosine as previously described. Noradrenaline acts primarily on α-receptors to cause intense arteriolar and venous vasoconstriction, usually accompanied by a reflex bradycardia. Noradrenaline is also an agonist at β-adrenoceptors and therefore falls in to the class of 'ino-constrictors', alongside the other endogenous catecholamines. Noradrenaline

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