Adenosine: an importance beyond ATP

Adenosine is familiar as a component of the ubiquitous intracellular energy store adenosine triphosphate (ATP) and the intracellular second messenger 3′,5′-adenosine monophosphate (cyclic AMP), but the extensive biological activity of the free nucleoside is less widely recognised and was the subject of a recent international symposium in Munich. 1

Newby has emphasised that many effects of adenosine may be viewed as controlling the balance between local energy (or oxygen) supply and demand. 2 When energy supply and demand are out of balance ATP breakdown is increased, and some of the metabolites reach the extracellular space as adenosine. 3 4 Adenosine released in this manner tends to increase energy supply (often through vasodilatation) or reduce energy demand, or both—and so tends to restore the tissue energy balance.

Adenosine exerts such a homeostatic role in the metabolic control of coronary blood flow. 5 Its release is augmented by increased myocardial work or impaired blood supply, 6 7 and it then increases coronary blood flow and the energy supply. Such feedback mechanisms allow the heart to adjust coronary blood flow to constantly varying demands; the importance of this process is shown when stenoses of the coronary arteries override metabolic control of coronary flow and produce angina and myocardial infarction. The precise circumstances in which, and to what degree, adenosine controls coronary flow are debated, 8 9 but the coronary vasodilator effect of adenosine has been confirmed in man. 10 11 Adenosine also slows cardiac rate and impairs conduction through the atrioventricular node, 12 13 and adenosine release during myocardial ischaemia 14 may explain the bradycardia-thrombocytopenia commonly seen in the early phases of myocardial infarction. 15 These cardiac electrophysiological effects of adenosine have been used in the acute treatment of supraventricular tachycardia 16 17: it restores sinus rhythm by interrupting re-entrant circuits involving the atrioventricular node. 18 Its extremely short half life (about 10 seconds) 19 makes it particularly useful when intravenous verapamil is contraindicated—for example, in patients with poor left ventricular function or those treated with β blockers. Adenosine is of little use, however, in preventing these arrhythmias.

Adenosine is also a peripheral vasodilator and has been used to produce controlled hypotension during cerebral artery surgery. 20 It produces hypotension smoothly, and the infusion rate can be titrated to give a stable blood pressure; normal blood pressure is rapidly restored after the infusion is stopped, without rebound hypertension. 21 22 The lack of rebound may be to do with adenosine inhibiting renin release. 23 An autoregulatory role for adenosine in controlling blood flow in the brain 24 and the skeletal muscle 25 has also been proposed, but the evidence is less extensive than that relating to coronary flow.

Renal blood flow, glomerular filtration rate, and salt and water clearance are all reduced by adenosine. 26 27 Renal energy demand depends largely on the volume of glomerular filtrate, 28 and so the vasoconstrictor effect of adenosine released in response to increased renal metabolic work reduces glomerular filtrate and hence energy demand.

By interacting with release of other neurotransmitters in the peripheral and central nervous system and by other presynaptic and postsynaptic actions adenosine (and the nucleotide ATP) modulate neural activity in the peripheral and central nervous system. 29 30 These effects are complex and subtle, but overall adenosine is a central nervous system depressant. Caffeine and other methylxanthines, which are antagonists at cell surface adenosine receptors, probably achieve their stimulant effect by reversing the central sedative actions of adenosine. 31 Adenosine may participate in the spontaneous termination of epileptic fits 32 and in the action of certain anticonvulsant drugs—for example, phenytoin 33—but further work is needed on these mechanisms.

Adenosine reduces platelet aggregation in vitro, 34 but its part in platelet function in vivo is uncertain. It has, however, been used to reduce platelet consumption during cardiopulmonary bypass. 35 Adenosine appears to be an important substrate for ATP synthesis in red cells; these have a circulating life of about 120 days, but the half life of ATP in erythrocytes (which cannot synthesise ATP de novo) is only about nine hours. 36 Adenosine released by the liver appears to play a significant part in replenishing erythrocyte ATP and so keeps red cells alive. 37 38

As well as having a local effect on oxygen balance adenosine is a respiratory stimulant in man. 39 40 This action is achieved through the carotid body in animals 41 and also, it seems, in man. 40 Adenosine release is intimately linked to control of local oxygen balance in other tissues, but the suggestion that adenosine may help to initiate the ventilatory response to hypoxia in the carotid body remains to be proved. 42

Adenosine may also be important in pathophysiological states. It is a bronchoconstrictor in asthmatic but not normal subjects. 43 The efficacy of aminophylline and other methylxanthines, which are antagonists at cell surface adenosine receptors, may be attributable to them antagonising adenosine in asthmatic subjects. 44

The physiological importance of endogenous adenosine
Primary pulmonary hypertension

Pulmonary hypertension is usually secondary to cardiac or pulmonary disease, and only rarely is it "primary" or "unexplained." At sea level for a cardiac output of 5-6 litres systolic pulmonary arterial pressure is about 20 mm Hg and diastolic about 12 mm Hg. In pulmonary hypertension the mean arterial pressure is above 19-20 mm Hg. Although right pulmonary hypertension is important because it affects young people and has a 10 year survival of only 25%. The diagnosis is often delayed as the signs of raised pulmonary vascular resistance without a cardiac cause, respiratory insufficiency, or collagen vascular disease may be missed. The diagnosis must be considered in breathless patients, particularly when associated with syncope and angina. Right heart failure develops late, but a loud pulmonary second heart sound is often heard. Signs of raised pulmonary vascular resistance on chest radiograph and electrocardiogram are found in 95% of cases. Spirometric values are normal, but gas transfer for carbon monoxide may be low. Doppler M mode echocardiography shows characteristic signs and allows an assessment of pulmonary arterial pressure and exclusion of a left to right shunt. Ventilation and perfusion lung scintigraphy can exclude prostatic vessel thrombembolism. Right heart catheterisation confirms the diagnosis and provides prognostic information: the lower the cardiac output the worse the prognosis. The most discriminating test is the mixed venous oxygen saturation: when it is less than 63% survival at five years is 17%, whereas when it is greater than 63% survival is as high as 55%. "Spontaneous" recovery may occur in those with high cardiac output. Surgical endarterectomy can improve the haemodynamic measurements in patients with longstanding proximal pulmonary arterial obstruction from thromboembolism. Diagnosis is with ventilation and perfusion lung scintigraphy and preoperative assessment requires pulmonary angiography.

In patients without proximal vessel obstruction the haemodynamic disturbance is a result of a "restriction" of the peripheral pulmonary vasculature, in contrast to the "vasoconstriction" of hypoxia. Idiopathic pulmonary hypertension is associated with a generalised loss in the precapillary non-muscular vessels. whereas in patients with primary pulmonary hypertension and peripheral thrombosis muscular and non-muscular arteries are obstructed in a patchy distribution. Adaptive dilatational lesions

Andrew H Watt
Clinical research officer

Philip A Routledge
Senior lecturer

Department of Pharmacology and Therapeutics,
University of Wales College of Medicine,
Cardiff CF4 4XN