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Adenosine Triphosphate
Established and Potential Clinical Applications

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Contents

Abstract

Adenosine 5′-triphosphate (ATP) is a purine nucleotide found in every cell of the human body. In addition to its well established role in cellular metabolism, extracellular ATP and its breakdown product adenosine, exert pronounced effects in a variety of biological processes including neurotransmission, muscle contraction, cardiac function, platelet function, vasodilatation and liver glycogen metabolism. These effects are mediated by both P1 and P2 receptors. A cascade of ectonucleotidases plays a role in the effective regulation of these processes and may also have a protective function by keeping extracellular ATP and adenosine levels within physiological limits. In recent years several clinical applications of ATP and adenosine have been reported. In anaesthesia, low dose adenosine reduced neuropathic pain, hyperalgesia and ischaemic pain to a similar degree as morphine or ketamine. Postoperative opioid use was reduced. During surgery,

ATP and adenosine have been used to induce hypotension. In patients with haemorrhagic shock, increased survival was observed after ATP treatment. In cardiology, ATP has been shown to be a well tolerated and effective pulmonary vasodilator in patients with pulmonary hypertension. Bolus injections of ATP and adenosine are useful in the diagnosis and treatment of paroxysmal supraventricular tachycardias. Adenosine also allowed highly accurate diagnosis of coronary artery disease. In pulmonology, nucleotides in combination with a sodium channel blocker improved mucociliary clearance from the airways to near normal in patients with cystic fibrosis. In oncology, there are indications that ATP may inhibit weight loss and tumour growth in patients with advanced lung cancer. There are also indications of potentiating effects of cytostatics and protective effects against radiation tissue damage. Further controlled clinical trials are warranted to determine the full beneficial potential of ATP, adenosine and uridine 5′-triphosphate.

Adenosine 5′-triphosphate (ATP) is a naturally occurring nucleotide which is present in every cell. It consists of a purine base (adenine), ribose and 3 phosphate groups. Nucleotides were first recognised as important substrate molecules in metabolic interconversions, and later as the building blocks of DNA and RNA. More recently, it was found that nucleotides are also present in the extracellular fluid under physiologic circumstances.[1] Extracellular ATP is broken down by a cascade of ectoenzymes and xanthine oxidase to form uric acid, which is excreted in urine (fig. 1).

Extracellular ATP appears to be involved in the regulation of a variety of biological processes including neurotransmission, muscle contraction, cardiac function, platelet function, vasodilatation and liver glycogen metabolism. ATP can be released from the cytoplasm of several cell types and interacts with specific purinergic receptors on the surface of many cells. These receptors play a fundamental role in cell physiology, and are divided into 2 major classes: P1 and P2 receptors. In general, the effects of adenosine are thought to be mediated through P1 receptors, whereas ATP binds to P2 receptors. P1 receptors are subdivided into A_1, A_{2A}, A_{2B} and A_3 receptors[2] which activate phospholipase C (A_1, A_{2B}, A_3) and adenylate cyclase (A_{2A}, A_{2B}), and modulate ion channels (A_1, A_{2B}, A_3).[3] P2 receptors are subclassified in G-protein–coupled receptors termed P2Y receptors and intrinsic ion channels termed P2X receptors.[2,4] Stimulation of the various receptors evokes diverse biological responses and has been reviewed by Dubyak and el-Moatassim[5] and Conigrave and Jiang.[6]

In recent years the possible pharmacological uses of ATP have received attention, following reports of its potential benefit in pain, vascular diseases and cancer (table I). In this review, current and potential clinical applications, and proposed mechanisms of action of extracellular ATP and its breakdown product adenosine (fig. 2), are discussed together with their pharmacokinetic properties and adverse effects.

1. Pharmacokinetic Properties

1.1 Physiological Levels

The average physiological level of ATP within mammalian cells is 3152 ± 1698 (SD) μmol/L. The ATP content in tissue cells is somewhat higher than in blood cells.[7] In human erythrocytes ATP levels of 1500 to 1900 μmol/L are detected.[8-10] Only 3 authors have reported ATP levels in human plasma. Forrester and Lind[1] described levels of 1.2 ± 0.5 μmol/L, while Harkness et al.[11] measured 3.9 ± 1.5 μmol/L ATP, and Ryan et al.[12] reported a range of 0.15 to 0.65 μmol/L ATP. These concentrations are in the same order of magnitude as the physiological concentrations of adenosine in plasma, that is, 0.1 to 1 μmol/L.[13]

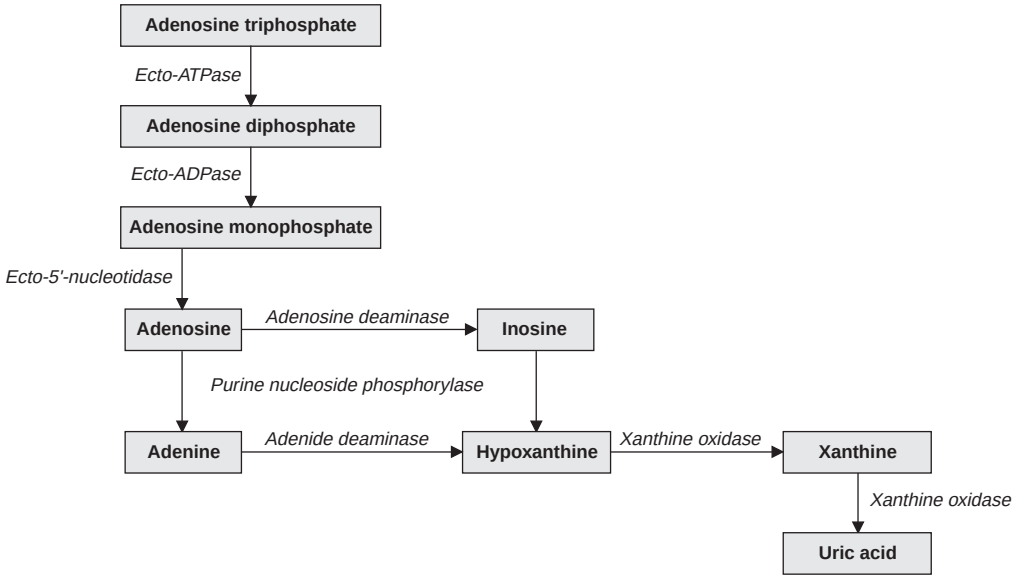

Fig. 1. Pathway of adenosine 5′-triphosphate (ATP) breakdown to uric acid.

1.2 Cellular Uptake and Transport

Using suspensions of washed intact human erythocytes and labelled purines, Parker[14] found that ATP is metabolised outside the cell via adenosine diphosphate (ADP) and adenosine monophosphate (AMP) to adenosine. Adenosine rapidly entered the erythrocytes where it was incorporated in adenine nucleotides. At extracellular adenosine concentrations below 3 μmol/L, most intracellular adenosine was phosphorylated to adenine nucleotides. At higher extracellular adenosine concentrations, adenosine was degraded in the erythrocytes to inosine and hypoxanthine.[15] Intravenous administration of ATP is followed by rapid uptake by erythrocytes.[16] In a study in patients with cancer, infusion of ATP 50 μg/kg/min, induced a 63% increase in whole blood ATP levels; a higher rate of ATP infusion of 75 μg/kg/min gave only a slightly greater increase (67%).[17]

After intraperitoneal bolus injection of adenine nucleotides in mice,[18] an increase in erythrocyte ATP levels (from 600 to 1700 μmol/L) was preceded by an increase in liver ATP (from 3000 to 700 0 μmol/L). The IP mode of administration of adenine nucleotides seems to favour uptake by the liver, presumably because they enter the portal circulation.[18] Lerner and Lowy[19] showed that rabbit liver perfused with [^{3}H]adenine released [^{3}H]adenosine. They suggested that adenosine may be released from liver cells into the interstitial fluid and then the hepatic sinusoids, where it would be rapidly taken up by the circulating erythrocytes and incorporated into adenine nucleotides. Within seconds after IP administration of unlabelled ATP and [^{3}H]adenosine, [^{3}H]ATP was found in plasma.[20] Rapaport[21,22] suggested that following rapid degradation of administered ATP, ATP is resynthesised in the liver, and then taken up by erythrocytes from which it is subsequently slowly released into plasma resulting in micromolar plasma levels of ATP.

1.3 Metabolism

Degradation of ATP in whole blood *in vitro* is considerably slower than under *in vivo* conditions. *In vitro*, 5 min after incubation of rabbit whole blood with ATP at 37°C, 93.2% of the ATP remained.[23] In contrast, in rabbits 40 seconds after

Table I. Effects of adenosine 5′-triphosphate (ATP) and adenosine with potential or demonstrated clinical implications

Topic	Cells/organs	Animals	Patients
Anesthesia and analgesia			
blood pressure during surgery			Reduced
anaesthetic requirement		Reduced	Reduced
opioid requirement after surgery			Reduced
pain		Reduced	Reduced
Pulmonary hypertension		Reduced	Reduced
Supraventricular tachycardias			Inhibited
SA + AV node conduction	Inhibited		Inhibited
Mechanism wide QRS complex			Diagnostic assessment
Coronary artery disease			Diagnostic assessment
Shock			
organ function	Improved	Improved	
survival rate		Increased	Increased
Airway mucosa function			
surfactant secretion	Increased		
chloride secretion[a]	Increased		Increased
ciliary beat frequency	Increased		
mucus secretion	Increased		
water secretion	Increased		
mucociliary clearance[b]			Increased
Metabolism			
gluconeogenesis	Reduced/increased		
glycogenolysis	Increased		
Cancer treatment			
weight loss		Inhibited	Inhibited
tumour growth	Inhibited	Inhibited	Inhibited
chemotherapy efficacy	Increased	Increased	
radiotherapy damage	Reduced	Reduced	
radiotherapy efficacy	Increased	Increased	
radiotherapy survival rate		Increased	

a Observed in epithelia of healthy participants and cystic fibrosis patients.

b Epithelia of cystic fibrosis patients.

AV = atrioventricular; **SA** = sinoatrial.

an intravenous bolus injection of ATP, only 1% of injected ATP was detected in whole blood.[23] Similarly, a bolus of ATP is almost completely cleared during a single passage through either perfused dog lung[24] or perfused guinea-pig heart.[25] Ryan and Smith[26] showed a half-life of ATP of less than 0.2 seconds in perfused rat lung. At physiological levels, the half-life of [^{3}H]adenosine in human plasma *in vivo* is 0.6 to 1.5 sec.[27]

A cascade of ectonucleotidases on the endothelial cells is thought to be responsible for the hydrolysis of ATP in blood *in vivo*.[26,28-30] There are 3 types of ectonucleotidases: ecto-ATPases, ecto-ADPases and ecto-5′-nucleotidases.[16] These enzymes have also been detected on a variety of other cell types including erythrocytes,[16] leucocytes,[31] B lymphocytes,[32] both helper and cytotoxic T lymphocytes (CTLs),[33] and hepatocytes.[34] The ectonucleotidase system could be of importance in the regulation of neurotransmission, blood-platelet function and vasodilatation.[29] It has also been suggested that ectonucleotidases on the surface of cell membranes may have a protective function by keeping extracellular ATP and adenosine levels within physiological limits.[16]

2. Physiological Effects and Mechanisms of Action

2.1 Nervous System

ATP acts as a neurotransmitter in both the central and peripheral nervous system and can also modulate the release of other neurotransmitters.[35] There is evidence that ATP plays a role as sensory neurotransmitter and adenosine as neuromodulator when both are released from non-nociceptive, large diameter, primary afferent neurons and capsaicin-sensitive, small diameter, primary afferent nerve terminals in the dorsal horn, and that adenosine in particular inhibits pain transmission.[36,37] It also seems likely that the effects of ATP on pain are dependent on ATP being broken down to adenosine.[36,38]

The antinociceptive effects are mediated through activation of A_1 and A_2 receptors.[36,37] These receptors are localised in the substantia gelatinosa of the spinal dorsal horn.[39-41] Based on the observation that the adenosine blockers theophylline and caffeine also partly inhibit the analgesic effects of morphine, it has been suggested that adenosine may be one of the intermediary substances involved in morphine-induced spinal antinociception.[36]

2.2 Respiratory System

Several cell types in both the upper and lower respiratory system respond to ATP and also to uridine 5′-triphosphate (UTP). In type II alveolar epithelial cells of newborn rats, ATP and UTP stimulate P2Y receptor–coupled surfactant secretion.[42,43] In airway epithelia of healthy individuals and patients with cystic fibrosis (CF), ATP and UTP stimulate transepithelial chloride secretion. Chloride is secreted through the CF transmembrane regulator (CFTR)[44-46] as well as the non-CFTR.[47-49] In this way, in nasal epithelial cells from CF patients, Knowles et al.[50] observed an increase in transepithelial potential difference. The magnitude of potential difference correlates with the rate of chloride secretion and sodium absorption. Several studies have demonstrated that the effects of ATP and UTP on chloride transport are mediated by a separate class of P2 receptors,[50,51] named $P2Y_2$ receptors.[52-54] Stimulation of these receptors activates inositol phospholipid hydrolysis and calcium mobilisation.[51]

ATP export from the mucosal cell has also been related to the CFTR gene product. It has been suggested that the CFTR functions directly as an ATP channel,[47,55,56] but this finding was recently rejected: Reddy and Quinton[49] and Reddy et al.[57] demonstrated that the CFTR is a regulator of an associated ATP channel.

2.3 Immune System

Lymphokine-activated killer (LAK) cells and CTLs are subtypes of effector lymphocytes which play an important role in immune defence against tumour cells and virus-infected cells. The mechanism by which LAK cells and CTLs lyse their target cells is a subject of intense interest. Since the early 1990s, ATP has been proposed as a possible mediator of cytotoxic cell–dependent lysis. ATP

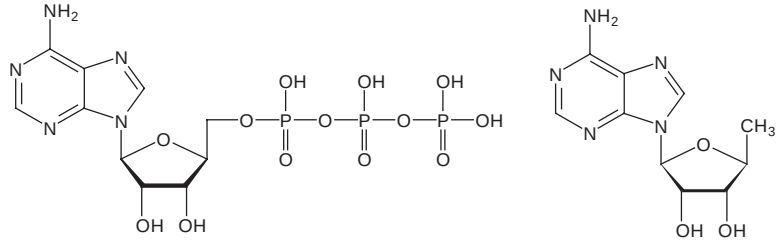

Fig. 2. Structural formulae of adenosine 5′-triphosphate (ATP) and adenosine.

could either be secreted via exocytosis, or directly released from the cytoplasm of LAK cells and CTLs by a yet unknown process.[58] Zanovello et al.[59] observed an ATP-induced calcium influx in classical natural killer target cells (YAC-1) and DNA fragmentation in P815 target cells. Both EL-4 lymphoma cells and multidrug resistant human colon carcinoma cells (LoVo-Dx) were sensitive to ATP, as well as to CTLs and LAK cells.[60-62] Filippini et al.[33,63] suggested that the lytic effects of ATP on CTL target cells may be the result of ATP on purinergic receptor or ectoprotein kinase (ecto-PK) stimulation.

CTLs and LAK cells, as putative sources of ATP, have been shown to be resistant to the lytic effects of ATP,[59,61,64,65] possibly because of the absence of purinergic receptors[61] and a high expression of ecto-ATPases.[61,65] These ecto-ATPases would effectively eliminate self-generated ATP from the LAK cell membrane.[64]

2.4 Blood Vessels

Both P1 and P2 receptors are present in blood vessel walls. Two subtypes of the P2 receptor have been described: P2X and P2Y receptors.[66,67] P2X receptors are located on vascular smooth muscle cells, and mediate vasoconstriction. P2Y and P1 receptors are located on endothelial cells, and mediate a vasodilator response,[68,69] and this vasodilation is probably responsible for a variety of the physiological effects of ATP.

When given intravenously, low dose ATP and adenosine have mainly pulmonary rather than systemic effects, because they are rapidly metabolised during their passage through the lung.[70] In the pulmonary circulation, the predominant types of purinergic receptors are the P2Y and P1 receptors.[71,72] ATP binds to the P2Y receptor on the pulmonary endothelial cell and stimulates the formation of nitric oxide (NO). NO increases the concentration of the intracellular messenger involved in smooth muscle relaxation, cyclic guanosine monophosphate (cGMP).[73,74] Adenosine binds to the P1 receptor on pulmonary endothelial cells, increasing endothelial-cell adenylate cyclase activity and cellular cyclic AMP (cAMP) level and causing vascular smooth muscle relaxation.[35,73]

2.5 Heart

In the sinoatrial (SA) and atrioventricular (AV) nodal cells, extracellular ATP and adenosine stimulate the release of potassium which induces an electric current and results in depression of the SA node as well as slowing down the AV node conduction.[75-79] ATP is thought to induce the effects after degradation to adenosine.[31] Their electrophysiological effects are mediated by activation of extracellular A_1 receptors which are coupled with guanosine triphosphate–binding inhibitory proteins. Dipyridamole, an inhibitor of adenosine transport across cell membranes, potentiates these effects, while methylxanthines, such as theophylline and caffeine antagonise the activities of the adenosine receptors. Stimulation of the A_1 receptor influences both the potassium channels and cAMP production.[80]

Some authors have postulated that the nodal effects of ATP are modulated by atropine, suggesting that these effects may partly be mediated through muscarine receptors of the vagal nerve.[81,82] Recently, Tai et al.[83] demonstrated that during use of atropine, patients required a higher dose of adenosine to terminate tachycardia. However, in other studies atropine did not influence the cardiac effects of ATP and adenosine.[84,85]

2.6 Liver

Extracellular ATP induces phosphatidylinositol hydrolysis and Ca^{++}-mobilisation and influx in isolated hepatocytes.[86-88] This has been ascribed to stimulation of P2 receptors.[86,87,89,90] Koike et al.[91] showed that the rise in intracellular calcium plays an important role in triggering gluconeogenesis. Depending on the concentration, extracellular ATP can either stimulate or inhibit gluconeogenesis in isolated hepatocytes. Maximal stimulation of gluconeogenesis was shown at 40[92] and 100 μmol/L ATP.[90,91,93] Maximal inhibition was shown at 1000 μmol/L ATP[94] and 500 μmol/L adenosine.[95]

The increase in hepatocyte calcium levels is also associated with increased glycogenolysis.[86,96-98] Studies in perfused rat livers have been confirmed the stimulating effects of ATP on glycogenolysis.[99]

2.7 Tumour Cells

ATP has cytostatic and cytotoxic effects in many types of transformed and tumour cells. Several mechanisms have been proposed:

1. Exposure of human adenocarcinoma cells to extracellular ATP has been reported to cause intracellular accumulation of ATP and arrest of tumour cells in the S-phase of cell replication, followed by cell death.[100] A similar ATP-induced growth inhibition, caused by prolonging of the S-phase, is found in rat ureter carcinoma cells[101] and in human breast cancer cells.[102] Weisman et al.[103] showed that extracellular ATP was hydrolysed to extracellular adenosine which was transported into the cells by adenosine translocators.

2. Intracellular adenosine induced growth inhibition by elevating intracellular ATP and ADP and reducing intracellular UTP levels. These changes induced inhibition of pyrimidine nucleotide biosynthesis. Based on this, it was suggested that the inhibition of tumour growth after exposure to extracellular ATP is caused by an adenosine-dependent pyrimidine starvation effect.[103-105]

3. ATP-induced tumour growth inhibition is associated with lower rates of protein synthesis and lower γ-glutamylcysteine synthase activity.[104] The latter leads to a decrease in glutathione content of the tumour, but not of normal tissues.[104-106]

4. Protein phosphorylation catalysed by a number of cell surface protein kinases is known to occupy a key role in transmembrane signal transduction. Friedberg and Kuebler[107] and Friedberg et al.[108] showed a positive correlation between the activity of ecto-PK and the ability of ATP to induce cell growth inhibition. Removal of this enzyme prevented ATP-induced growth inhibition. A growth inhibitor, a protein with an apparent molecular mass of 13 kDa, is produced on exposure to extracellular ATP. Transformed cells have a higher activity of ecto-PK compared with nontransformed cells.[107,108]

5. After ATP administration, increased membrane permeability has been demonstrated in various transformed cells, including fibroblasts,[107,109-112] ovary cells,[113] melanoma cells,[112,114] neuroblastoma cells,[115] hepatoma cells,[116] hepatocytes,[117,118] erythroleukaemia cells,[119] mastocytoma cells,[33] lymphoma cells[58,59,64,120] and leukaemic lymphocytes.[121-123] In contrast, this increase in permeability was not observed in untransformed cells.[107,109,112,114,121,124] Although in these studies no systematic search for receptors was undertaken, the evidence suggests that increased cell permeability after exposure to extracellular ATP may be caused by activation of $P2X_7$ (formerly P2Z) receptors.[125,126] These receptors are highly selective for the tetrabasic ATP^{4-} form.[127] The tumour cell types that express these receptors on their cell surfaces include various leukaemia cells[127-130] and neuroblastoma cells.[131] Activation of the $P2X_7$ receptors causes opening of ion channels which leads to an increase of intracellular Ca^{++}, loss of K^+, entry of Na^+ and a decrease in the membrane potential. Activation of $P2X_7$ receptors also results in formation of nonselective pores, which induces an increase in nonselective membrane permeability for aqueous solutes that ordinarily do not cross the cell membrane, including nucleotides and small hydrophilic molecules of molecular weight up to 900Da.[132] In transformed 3T6 mouse fibroblasts Saribas et al.[133] found that ATP increases the permeability to molecules as large as 20 kDa. Opening of these ATP-sensitive channels or ATP-induced pores will lead to cell death either by cell swelling, which is characteristic for necrosis,[111,132] or DNA fragmentation, which is characteristic for apoptosis.[59,120]

Beyer and Steinberg[134] showed that pore formation in macrophages is the result of damage to the gap junction protein connexin-43. Loewenstein[135] confirmed these results and reported that connexin-43 is more exposed in neoplastic cells than in normal cells. Neoplastic cells are known to be deficient in intercellular communication and

therefore have gap junction proteins which are exposed to the extracellular environment.[134,135] It has been suggested that connexin-43 may have a function as a 'suicide receptor'.[135] However, Alves et al.[136] recently were unable to show an effect of extracellular ATP on connexin-43 hemigap-junction channels, thus contradicting the findings of Beyer and Steinberg.[134]

2.8 Tissue Protection

Under conditions of metabolic stress, such as ischaemia, a rapid and massive depletion of intracellular ATP occurs. As a consequence of ATP breakdown, adenosine, inosine and hypoxanthine accumulate in the ischaemic tissue.[137,138] Bouma et al.[139] proposed that adenosine may exert protective effects during the reperfusion period by binding to A_2 and A_3 receptors. In this context, Newby[140] introduced the term 'retaliatory metabolite' and Bouma et al.[141] described adenosine as part of a 'natural defence system'. The protective action of adenosine or ATP can be explained by cardiovascular, metabolic and anti-inflammatory activities, as studied under *in vitro*, *in vivo* and clinical conditions.

The cardiovascular effects of ATP seem important in improving flow after ischaemia. In animal models of shock, intravenous ATP-$MgCl_2$ enhances the renal[142] and hepatic microcirculation,[143-145] portal and total hepatic blood flow,[146] and cardiac output.[147]

ATP-induced metabolic effects include improved mitochondrial function and electrolyte transport, increased intracellular ATP,[148-150] reduced O_2 consumption,[151] enhancement of P2 receptor-binding capacity[152] and normalisation of impaired second messengers cAMP and inositol 1,4,5-triphosphate (IP_3).[153]

The inhibitory effects of adenosine extends to different processes related to inflammation:

- inhibition of effectors – neutrophil superoxide production, neutrophil degranulation,[139] and antioxidants activation[154,155]
- inhibition of mediators – tumour necrosis factor (TNF), interleukin (IL)-6,[156,157] IL-8,[157,158] eicosanoids[159] and complement[160]
- inhibition adhesion of neutrophils,[161] inhibition of adhesion molecule expression.[158]

Furthermore, Cronstein et al.[162] demonstrated that the antiphlogistic action of the potent anti-inflammatory agent methotrexate is caused by increased adenosine release at inflamed sites. The increase in extracellular adenosine diminishes both the accumulation and function of leucocytes in inflamed sites.

3. Clinical Applications

3.1 Anaesthesia

3.1.1 Pain Reduction

During the last decade, studies in both animal models and patients have shown that ATP and particularly adenosine at low doses may modulate pain. Intravenous ATP in mice was found to have a dose-dependent analgesic activity on hot plate and phenylquinone-induced stretching assays.[36,37,163] In dogs, when adenosine was used in combination with halothane, halothane requirement was reduced by 49%.[164]

Several double-blind, placebo-controlled, cross-over studies in healthy volunteers showed pain-reducing effects of intravenous adenosine infusion 50 to 70 μg/kg/min. Segerdahl et al.[165] observed a reduction in size of the tactile allodynic area by approximately 50%. They also reported ischaemic pain-reducing effects of intravenous adenosine (70 μg/kg/min during 30 min) comparable with morphine (20 μg/kg/min during 5 min) or ketamine (20 μg/kg/ min during 5 min). Furthermore, adenosine given in combination with morphine or ketamine had an additive effect on pain reduction.[166]

In 2 randomised, double-blind studies in patients undergoing breast surgery (75 patients)[167] and gynaecological abdominal surgery (43 patients),[168] a systemic adenosine intravenous infusion (80 μg/kg/min) significantly reduced perioperative isofluorane requirements and postoperative pain. In addition, in both studies the need for opi-

oids was reduced by approximately 25% in the adenosine group during the first 24 postoperative hours.[167,168]

Several reports have provided evidence that low dosages of adenosine (50 μg/kg/min) alleviate neuropathic pain, hyperalgesia and allodynia without inducing other pain symptoms.[169,170] Intravenous adenosine infusion for 45 to 60 min led to improvement of spontaneous or evoked pain in 6 out of 7 patients with peripheral neuropathic pain, which lasted from 6 hours to 4 days.[169] This positive finding was unexpected since it is known that adenosine is rapidly eliminated from the blood. It was speculated that the effects of adenosine on central hyperexcitability persist longer than the direct action of adenosine on the receptors.[170]

3.1.2 Shock

A common feature of shock is an inadequate circulation with diminished perfusion of tissues, resulting in hypoxia and injury to various tissues. The resuscitation period after shock is also associated with development of tissue injury and loss of organ function.[141]

Several *in vivo* animal studies show that following haemorrhagic shock, infusion of ATP-$MgCl_2$ has a positive effect on survival.[144,145,149,150,171-175] Various studies indicate that ATP and adenosine have protective effects on tissue injury following reperfusion after a preceding period of ischaemia. ATP-$MgCl_2$ improves rat kidney,[176,177] rat liver,[176,178] dog heart,[179,180] rabbit lung[181] and rat gut function[182] after a period of ischaemia. The use of intramuscular ATP-$MgCl_2$ is also protective in rats with burns.[172]

In patients with acute renal failure or multiple organ failure, beneficial effects of ATP-$MgCl_2$ were observed in a single study. 32 patients were randomly divided into 2 groups. One received intravenous ATP-$MgCl_2$ (40 to 50 μmol/L/kg) and the other served as a control. The survival rate was 100% in the ATP group and 73.3% in the control group.[183]

3.1.3 Control of Blood Pressure

ATP and adenosine have been used to cause hypotension during anaesthesia and surgery in patients. Already, in 1951, Davies et al.[184] showed in patients that an intravenous or intra-arterial injection of 40mg ATP induced a moderate fall in blood pressure without change in heart rate. Controlled hypotension may be employed to reduce intraoperative haemorrhage. The haemodynamic effects of ATP and adenosine have been investigated in over 150 patients undergoing oral,[185] orthopaedic,[186] abdominal aortic aneurysm,[187,188] cerebral aneurysm[189-192] and unspecified surgery.[193,194] IV ATP or adenosine infusion (50 to 350 μg/kg/min) induced significant reductions in blood pressure (20 to 43%) with a major decrease in systemic vascular resistance (36 to 67%) and increase in cardiac output (14 to 42%), and only a small increase in heart rate (3 to 16%). The haemodynamic parameters returned to their baseline values immediately after stopping the infusion.[193,194] Tachyphylaxis and rebound-hypertension were not observed.[187,189-191,193-195] In contrast, Segerdahl et al.[167,196] showed no change in blood pressure during treatment with adenosine 80 μg/kg/min in patients with abdominal, breast and shoulder surgery. The reason for this discrepancy is not clear.

ATP and adenosine (150 to 300 μg/kg/min intravenously) have been used successfully during surgery for phaeochromocytoma to reduce systemic blood pressure.[197-199] ATP has been used to antagonise the vasoconstrictive activities of noradrenaline (norepinephrine) and/or sympathetic nerve stimulation.[197] Low dose adenosine intravenous infusion (30 to 50 μg/kg/min) in patients undergoing bypass surgery evoked coronary vasodilatation with only minor effects on the systemic circulation, and, therefore, may possibly be useful in the prevention of early occlusion of coronary artery bypass grafts.[200]

3.2 Cardiology

3.2.1 Pulmonary Hypertension

Pulmonary hypertension can be a serious problem after thoracic surgery in patients with chronic obstructive pulmonary disease (COPD), and in children with congenital heart defects. Vasodila-

tors have often been unsuccessful, because they act simultaneously on pulmonary and systemic vessels with predominant systemic effects.[201] However, low dose intravenous ATP or adenosine have been shown to exert predominant pulmonary vasodilating effects.[202,203]

In newborn lamb models, intravenous ATP was effective against pulmonary hypertension.[204-206] Several studies showed a predominant decrease in pulmonary arterial pressure during intravenous infusion of about 100 μg/kg/min ATP, while systemic arterial pressure and vascular resistance decreased at higher levels.[202,205,207,208]

Studies in healthy individuals,[70,209] patients with COPD[202,210,211] and children with pulmonary hypertension,[212] showed significant decreases in mean pulmonary arterial pressure and pulmonary vascular resistance during intravenous ATP infusion (to 100 μg/kg/min), without a change in mean systemic arterial pressure and systemic vascular resistance. In 7 children with pulmonary hypertension after surgical repair of congenital heart defects, ATP induced a decrease in pulmonary arterial pressure; 3 children showed complete disappearance of pulmonary hypertensive crises.[212] The children did not have rebound pulmonary hypertension,[212] although in some studies this effect was reported after discontinuation of ATP.[208,210] Recently, the effectiveness of intravenous ATP treatment against pulmonary hypertension has also been shown in 20 patients with septal defects during cardiac surgery.[213]

Fullerton et al.[203] reported 2 patients with acute life-threatening pulmonary vasoconstriction after thoracic surgery. In both, when standard treatment had failed, adenosine (25 to 50 μg/kg/min intravenously) achieved lowering of pulmonary arterial pressure without lowering of systemic arterial pressure.

3.2.2 Supraventricular Tachycardias

The antiarrhythmic effects of purines have been known for decades. In 1929, Drury and Szent-Gyorgi[214] described the effect of adenosine on myocardial conduction. The use of intravenous adenosine to terminate supraventricular arrhythmias was first described in 1933 by Jezer et al.[215] In 1955, Somlo[216] reported the first successful clinical trial with ATP in paroxysmal tachycardias.

There has been renewed interest in potential cardiac applications of ATP and adenosine in recent years. Several studies have demonstrated efficacy of intravenous ATP and adenosine in paroxysmal supraventricular tachycardia (PSVT) in both children and adults. In a double-blind study in 39 patients during 68 episodes of supraventricular tachycardias, there was no difference in the clinical efficacy of ATP and adenosine.[217] The actions of ATP may be primarily mediated by its breakdown product, adenosine.[31,218] In newborn children, intravenous ATP[219,220] and adenosine administration[221,222] successfully stopped supraventricular tachycardias. In patients with adult PSVT, bolus injections of 5 to 20mg ATP or 6 to 12mg adenosine induced normalisation of heart rate in over 90% of them.[79,223-228]

Most authors described no difference in efficacy between adenosine and the standard therapy for PSVT, verapamil,[224,229-232] whereas some authors showed a significantly greater overall efficacy of adenosine than of verapamil: 89 *vs* 61%[227] or 100 *vs* 80%.[223] Moreover, adenosine elicited a much more rapid antiarrhythmic response than verapamil. Adenosine terminated tachycardia within only 30 sec,[221,222,227,231,233,234] whereas in 2 studies in which verapamil was given, it took 142[227] and 248 sec,[231] respectively, to terminate tachycardia. Thus, the efficacy of adenosine would appear to be at least equivalent to verapamil, with a considerably more rapid onset of action.

Adenosine has also been used as a diagnostic tool of wide QRS complex tachycardias where the mechanism was uncertain. Wide complex ventricular tachycardia is often misdiagnosed as wide complex supraventricular tachycardia with aberrancy. Use of verapamil in these misdiagnosed patients can result in severe hypotension and cardiac arrest.[235,236] Because of its specific action on AV nodal conduction, adenosine can help to differentiate between supraventricular tachycardia with aberrant conduction and ventricular tachycardia. In

facilitating this diagnosis, a positive response to adenosine had a sensitivity of 90% and a specificity of 94%, based on electrophysiological studies.[235-237]

3.2.3 Pharmacological Stress Test

Assessment of myocardial ischaemia and coronary artery disease is used in the evaluation of risk before major surgery, and to select patients for coronary angiography, percutaneous transluminal coronary angioplasty or coronary bypass graft surgery after acute myocardial infarction, in addition to assessment of atypical chest pain. Because many patients are unable to perform an adequate exercise stress test, noninvasive methods to evaluate coronary artery disease have been developed.[85] For several years, thallium-201 or technetium-99m sestamibi myocardial perfusion imaging by single photon emission computed tomography (SPECT) has been used. Because maximal dilatation is needed to produce optimal SPECT images, these imaging techniques are often performed during infusion of a vasodilator.

Several studies clearly demonstrate the potential diagnostic use of the vasodilators ATP and adenosine for detection of coronary artery disease, using coronary angiography as gold standard. The pharmacological stress test of ATP or adenosine (to a maximum of 140 μg/kg/min intravenously for 6 min) in combination with thallium-201 scintigraphy has an overall sensitivity of 83 to 88% and a specificity of 78 to 100%.[238-240] Technetium-99m sestamibi SPECT with adenosine had a sensitivity of 91 to 95% and a specificity of 70 to 75% in detecting coronary artery disease.[241,242]

Echocardiography in conjunction with adenosine-induced coronary vasodilatation also produced accurate results with a sensitivity of 75 to 81% and a specificity of 86 to 100%.[243,244] The sensitivity and specificity values of the adenosine stress tests are approximately similar to those currently obtained during exercise stress tests.[241,245]

3.3 Pulmonology

3.3.1 Cystic Fibrosis

CF is an autosomal recessive disease characterised by an excessive production of airway secretions, resulting in bronchial obstruction and recurrent episodes of respiratory tract infections. Electrolyte transport across the airway epithelia is abnormal: excessive sodium absorption and defective regulation of the apical membrane chloride channel result in decreased water secretion and in increased reabsorption of periciliary fluid caused by decreased mucociliary transport. Furthermore, chloride secretion through the CFTR-chloride channel is absent.[246,247]

Because therapeutic agents are not available to improve chloride secretion in airways of CF patients, nucleotides have been tested. In normal as well as in CF airway epithelia, ATP induced chloride secretion.[44,46,51] ATP and also UTP evoked stimulation of ciliary beat frequency[247,248] and mucus secretion by goblet cells.[249-252] ATP and UTP also induced net water secretion across excised airway tissues.[253,254] It is possible that the endogenous triphosphate nucleotides may serve as coordinating factors of the airway clearance system.[255]

Knowles et al.[50,256] studied the effects of inhaled aerosolised ATP and UTP in 9 healthy individuals and 12 CF patients. These authors showed an ATP- and UTP-induced chloride secretion, with a maximal effective concentration at 100 μmol/L. The efficacy of both ATP and UTP was greater in CF patients than in healthy individuals.[256] Extracellular UTP may be a potentially better agonist than ATP, because the nucleoside breakdown product of ATP, adenosine, is a bronchoconstrictor of human airways.[255,257] In a study in 14 CF patients, the administration of inhaled UTP/amiloride combination was also demonstrated to improve mucociliary clearance from the peripheral airways of CF lungs to near normal basal rates.[258] The sodium channel blocker amiloride has been shown to effectively inhibit sodium absorption by respiratory epithelium.[246,259] These data support the concept for the use of UTP in combination with amiloride

as a therapy to improve clearance of secretions from the bronchi of patients with CF.

3.4 Oncology

3.4.1 Cancer Cachexia

Cancer cachexia is a syndrome of progressive weight loss associated with depletion of liver and skeletal muscle energy stores.[260] This depletion is caused by elevated lipolysis,[261,262] protein breakdown[263,264] and gluconeogenesis.[265-267] Dietary[268,269] and enteral supplements[269] fail to reverse the cachexia. In liver tissue[260,270,271] and in skeletal muscle[260] of tumour bearing rats, significantly lower ATP levels have been demonstrated, and this is associated with an increased gluconeogenesis.[271]

Administration of ATP and adenosine to a suspension of isolated hepatocytes inhibited gluconeogenesis from lactate and pyruvate, but not from glycerol or fructose. *In vivo*, daily IP injections of 25 mmol/L ATP, AMP or adenosine for 10 consecutive days into mice bearing colon tumours, induced a significant inhibition of host weight loss.[18,20] This inhibition was associated with expansion of hepatic ATP pools.[18] Rapaport[22] suggested that ATP may inhibit Cori cycle activity (i.e. the gluconeogenesis from lactate followed by reconversion of glucose to lactate in peripheral tissues), which is a potential means of inhibiting weight loss.

In the US, a phase I/II trial was recently carried out in stage IIIB/IV patients with nonsmall cell lung cancer (n = 8). After treatment with 2 to 3 intravenous ATP courses of 96 hours at 4-week intervals, stabilisation of bodyweight was observed.[17] In a subsequent open-ended phase II trial (n = 15), an average weight gain of 1.3kg was demonstrated after 4 ATP courses.[272] Despite the small sample sizes, these data suggest that ATP may have modulating effects on weight loss in cancer patients.

3.4.2 Inhibition of Tumour Growth

Extracellular ATP can modulate the growth of neoplastic cells *in vitro*. Below 100 μmol/L,[55,100,103] from 100 to 500 μmol/L,[102,114,273,274] from 500 to 1000 μmol/L[102,120] and above 1000 μmol/L,[120,275,276] extracellular ATP exerted cytostatic and cytotoxic effects on many transformed cell lines. In general, these effects appear to be greater than the effects on nontransformed mother cells.

In animal cell lines, ATP inhibited the growth of transformed fibroblasts,[103,112,277] leukaemia cells,[119,275,276] mastocytoma cells,[33] lymphoma cells,[64] thymocytes,[120] melanoma cells[114] and ureter carcinoma cells.[101] In human cell lines, ATP inhibited the growth of pancreatic carcinoma cells, colon adenocarcinoma cells,[21,100] melanoma cells,[100,112] androgen-independent prostate carcinoma cells,[273] breast cancer cells,[55,100,102,274] myeloid and monocytic leukaemia cells[128] and multidrug resistant colon carcinoma cells.[61] Similar exposure of nontransformed cell lines to ATP produced relatively less inhibition of cellular growth compared with transformed cells, or no inhibition at all.[100,112,114,275,276]

Hatta et al.[276] revealed the possibility of *ex vivo* purging of leukaemia cells by ATP in autologous bone marrow transplantation. Mice injected with an untreated mixture of normal marrow cells and L1210 leukaemia cells (10:1) died of leukaemia within 18 days. In contrast, 85% of the recipients given ATP-treated mixture cells survived for more than 70 days.

In mice with CT26 colon tumours, daily IP bolus injections of ATP (25 to 50 mmo/L) significantly inhibited tumour growth.[18,20-22] ATP-induced growth inhibition was also demonstrated in rats with ureter carcinomas,[278] mice with lymphomas,[279] fibrosarcomas,[280] Ehrlich ascites tumours[104,281] and breast tumours.[55] Furthermore, intraperitoneal ATP administration resulted in a significantly prolonged survival of these animals.[104-106]

Recently, in an open-labelled phase II study, 15 untreated patients with advanced nonsmall cell lung cancer (stage IIIB/IV) received 1 to 4 intravenous ATP courses (50 to 65 μg/kg/min for 96 hours), administered at 4-week intervals. No complete or partial tumour responses to ATP were reported, although stable disease was found in about two-thirds of the patients during the courses of

treatment.[272] No further studies on ATP as a single anticancer agent in humans are available.

3.4.3 Chemotherapy

In cancer cell lines, ATP may enhance the efficacy of several chemotherapeutic agents. Addition of 200 to 500 μmol/L ATP to doxorubicin in cultures of human ovarian carcinoma cells doubled the cell mortality, when compared with doxorubicin alone. 30 to 50% more doxorubicin accumulated in the cancer cells when given together with ATP, whereas in healthy human fibroblasts practically no effect of ATP on doxorubicin uptake was observed.[282] Furthermore, in transformed Chinese hamster ovary cells (CHO-K1), the presence of 100 to 500 μmol/L ATP and vinblastine or vincristine induced passive permeability of deoxy[^{3}H]glucose, while the drugs alone did not induce this change.[124] In mouse melanoma cell lines (clone-M3), 500 μg/kg/min ATP administration markedly increased the passive permeability for chemotherapeutic agents such as fluorouracil, doxorubicin, mitomicin and nimustine. The cytotoxic effects of these chemotherapeutic agents were additively potentiated by treatment with ATP. Vincristine combined with ATP showed even a synergistic cytotoxic effect; the effective concentration of vincristine was lowered 10- to 50-fold by ATP treatment.[114]

Recently, a tendency of potentiating effects of cytostatic agents was also observed in 1 study *in vivo* after administration of adenosine. In mice inoculated with B-16 melanoma cells, adenosine (5 mmol/L) was injected 5 days before administration of cyclophosphamide (50 mg/kg). This combined treatment reduced the number of melanoma foci by 60%, while the chemotherapy alone only reduced them by 45%. Moreover, a protective effect of adenosine against chemotherapy-induced decrease of leucocyte counts was seen in this study.[283] The use of ATP in combination with other agents for patients has been proposed, but no studies have been published.

In the treatment of acute myeloid leukaemia, a combination of interferon-γ and ATP might provide a potential chemotherapeutic regimen. In bone marrow blast cells obtained from patients with acute myeloid leukaemia, a dose-dependent lysis of malignant cells by ATP was demonstrated.[128] Furthermore, it was suggested that ATP might provide substantial benefit for chemotherapeutic treatment of brain tumours. In patients with malignant glioma selective enhancement of intratumoural blood flow after intercarotid administration of 0.5 to 1.3 μg/kg/min ATP was reported. It was hypothesised that in this way, greater amounts of cytostatic drugs might be transported into the brain tumour, without harming healthy brain tissue.[284]

3.4.4 Radiotherapy

Radiation causes DNA bond breakage and rearrangement. Because of radiation damage, tissue levels of the lytic enzyme acid phosphatase and the neurotransmission enzyme cholinesterase are increased. In contrast, the activities of the glycolytic key enzymes hexokinaseandlactate dehydrogenase are drastically decreased.[285] Stress such as by radiation in a living organism, may cause an increased demand for energy and glucose to repair damaged tissues.[286]

It has been suggested that extracellular ATP may provide energy for cellular repair processes.[287] Several studies have shown protection of ATP against damage caused by irradiation. Administration of ATP decreased the activities of acid phosphatase[288] and cholinesterase,[289] and augmented the activities of hexokinase and lactate dehydrogenase.[288] Moreover, it has been demonstrated that exogenous ATP may stimulate glycogenolysis[99] and glucose production in perfused liver of non-irradiated rats.[290]

In various animals, including mice and monkeys, the protecting effects of intramuscular or intraperitoneal ATP injections against radiation damage enhanced survival rates from 5 to 50%,[291] 4 to 40%,[292] 40 to 85%[285] and from 26 to 86%.[288] In addition, Senagore et al.[293] demonstrated that intravenous ATP-$MgCl_2$ infusion (60 μmol/L/kg) in pigs offered significant cytoprotection from pelvic radiotherapy. ATP infusion lead to diminished colorectal seromuscular ischaemia, decreased skin

and subcutaneous tissue injury and significantly decreased perianastomotic inflammatory reaction.[293]

Furthermore, when radiation was given in combination with ATP, the frequency of formation of aberrant mitoses in epithelial cells of the mouse cornea was lower than when no ATP was given.[294] Moreover, this combination reduced the tumour growth rate of transplanted fibrosarcomas in mice[280] and led to significant regression of Ehrlich ascites tumours in mice.[105]

4. Adverse Effects

In general, ATP and adenosine, when given as either a continuous intravenous infusion or by intravenous bolus administration, induce similar adverse effects. Adverse effects of ATP and adenosine include general discomfort,[231] breathing deeper or more frequently,[184,224,295-298] headache,[224,239,299] flushing, chest pressure or chest pain, and nausea.[217,224,225,227,235,239,295,300,301] Sinus bradycardia[224,235] and atrial fibrillation[228,302] have been observed in patients receiving a bolus of adenosine. The respiratory stimulation started before chest discomfort and showed characteristics of adenosine receptor mediated responses.[298] The chemoreceptors of the carotid artery wall are described as the most likely site of these responses.[297,303] Studies to characterise chest pain demonstrated that higher concentrations of adenosine increased the intensity of the pain.[300] The chest pain provoked by adenosine is angina-like, but electrocardiogram signs of myocardial ischaemia are absent. The algogenic effect of adenosine is related to activation of peripheral nociceptive afferents.[304-309] In angina pectoris, adenosine may be involved as an early messenger between myocardial ischaemia and pain.[306] Methylxanthines reduce this pain significantly,[300,306,308] while dipyridamole just increases the intensity of pain.[300,306]

The adverse effects with bolus administration of ATP and adenosine are generally mild and transient because of the short plasma half-life (0.6 to 1.5 sec).[27] Frequent dosage titration is possible because of the rapid adenosine clearance in plasma.[85]

Clinical studies with continuous incremental adenosine infusions, used for the provocation of pain and for the diagnosis of myocardial ischaemia, revealed that an adenosine infusion above approximately 75 μg/kg/min is associated with angina-like pain symptoms.[308-311] During intravenous ATP infusion in a phase I study in patients with advanced cancer, Haskell et al.[17] observed a cardiopulmonary reaction, typically characterised as a combination of a feeling of chest tightness without frank pain, and a sensation of 'needing to take a deep breath'. No significant haematological toxicity was noted. The most appropriate dosage of ATP in patients with advanced cancer was 50 μg/kg/min. Adverse effects during intravenous infusion resolved within seconds after discontinuing the ATP infusion.

As reviewed by Faulds et al.,[85] rapid intravenous bolus administration of adenosine induced transient haemodynamic effects, which were usually mild at doses at which ATP induced electrophysiological activity. IV adenosine infusion usually induced a small but significant increase in heart rate, small variations in systolic blood pressure, and a small but significant decrease in diastolic blood pressure and mean arterial pressure in conscious patients and volunteers.

5. Conclusion

ATP, adenosine and UTP have been shown to have a wide variety of beneficial effects in various clinical situations. The effects are probably mediated by P1 and P2 receptors. ATP, adenosine and UTP have been found to have potential in the management of pain, cancer, and some cardiovascular and pulmonary diseases. Much work still needs to be done to define the full range of indication for their compounds, their interactions with other drugs and ideal dosage schemes. P1 and P2 receptors are also potential targets for novel agonists and antagonists.

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