Potential value of adenosine 5'-triphosphate (ATP) and adenosine in anaesthesia and intensive care medicine

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Extracellular adenosine and adenosine triphosphate (ATP) are involved in biological processes including neurotransmission, muscle contraction, cardiac function, platelet function, vasodilation, signal transduction and secretion in a variety of cell types. They are released from the cytoplasm of several cell types and interact with specific purinergic receptors which are present on the surface of many cells. This review summarizes the evidence on the potential value and applicability of ATP (not restricted to ATP–MgCl2) and adenosine in the field of anaesthesia and intensive care medicine. It focuses, in particular, on evidence and roles in treatment of acute and chronic pain and in sepsis. Based on the evidence from animal and clinical studies performed during the last 20 years, ATP could provide a valuable addition to the therapeutic options in anaesthesia and intensive care medicine. It may have particular roles in pain management, modulation of haemodynamics and treatment of shock.


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Extracellular adenosine and adenosine triphosphate (ATP) are involved in biological processes including neurotransmission, muscle contraction, cardiac function, platelet function, vasodilation, signal transduction and secretion in a variety of cell types. They are released from the cytoplasm of several cell types and interact with specific purinergic receptors which are present on the surface of many cells. Recently, established and potential clinical applications of adenosine, ATP in general and ATP–MgCl2 in intensive care medicine have been reviewed separately. In this review, we summarize the evidence for the potential value and applicability of ATP (not just ATP–MgCl2) and adenosine in the field of anaesthesia and intensive care medicine. In particular, we have focused on results and treatment options for acute and chronic pain and for sepsis. Although a number of reports from animal and human studies show potential applications of adenosine and ATP in different clinical fields, including safety data, the application of both compounds in clinical practice is still very limited.

**Biology of adenosine and ATP**

Adenosine 5'-triphosphate (ATP) is the energy source in living cells. In physiological conditions, the average concentration varies from 3150 μM in mammalian cells to 1500–1900 μM in human blood cells. Plasma ATP concentrations ranging between 0.15 and 3.9 μM have been reported by different groups. In vivo, ATP is metabolized rapidly, via adenosine diphosphate (ADP) and adenosine monophosphate (AMP), to adenosine. Reported physiological plasma concentrations of 0.1–1 μM for these derivatives are of the same order of magnitude as for ATP.

A large family of membrane-bound receptors mediates cell signalling by ATP and adenosine. These purinergic receptors ultimately determine the variety of effects induced by extracellular ATP and adenosine. So far, two families of purinergic receptors have been identified, namely P1 and P2 receptors which respond principally to adenosine and ATP, respectively.

P1 receptors are G-protein coupled receptors, of which four types have been identified so far (A1, A2A, A2B, A3). Although all the P1 receptor subtypes are primarily activated by adenosine, each shows a different degree of affinity for its physiological agonists. Thus, besides adenosine itself, its breakdown product inosine has also been shown to exert an agonist action on A1 and A3 receptors, but not on A2 receptors. However, this agonist action of inosine appears to have a low efficacy compared with adenosine, especially at A3 receptors.

The P2 receptor family is divided in P2X and P2Y receptors, with a number of different subtypes which have varying...
affinities for ATP, ADP, uridine triphosphate (UTP), uridine diphosphate (UDP) and UDP–glucose.

P2X receptors are ligand-gated ion channels, of which currently seven subtypes have been characterized (P2X1–7). All are primarily activated by their physiological agonist ATP. P2Y receptors are G-protein coupled receptors, of which eight subtypes have been identified to date (P2Y1, 2, 4, 6, 11–14). In contrast with P2X receptors, P2Y receptor subtypes have specific agonist and affinity profiles. More specifically, P2Y receptors can be subdivided into two groups based on sequence homology. Group 1 consists of specific purinergic receptors (P2Y1, P2Y11), specific pyrimidinergic receptors (P2Y4, P2Y6) and receptors of mixed specificity (P2Y2). Group 2 contains two specific ADP receptors (P2Y12, P2Y13) and a recently identified receptor for UDP–glucose (P2Y14).

P1 and P2 receptors are widely distributed in body tissue. The extent of receptor expression on individual cells or in specific tissues partially determines the potency of receptor-mediated effects of ATP and adenosine.

Overall, signalling by P1 and P2 receptors depends on a wide variety of factors, such as receptor expression, receptor sensitivity for physiological agonists and extracellular levels of nucleotides/nucleosides. Purinergic signalling is even more complex in inflammatory conditions during which it is subjected to additional modulating factors, including the release of nucleotides/nucleosides. A schematic overview of different receptors is given in Figure 1.

Clinical effects of administration of adenosine and ATP
Continuous i.v. administration of ATP in humans induces a dose-dependent rise in ATP levels in erythrocytes and liver, followed by slow release into the plasma compartment. ATP levels in erythrocytes reach plateau levels at 24 h, and are significantly increased above baseline (more than 50%). At the same time, a significant increase in plasma uric acid concentration is observed. The mean half-life for the disappearance of ATP from erythrocytes is 5.9 h. Plasma concentrations are three orders of magnitude lower than within the erythrocytes, partly due to the rapid breakdown of ATP; only 1% of ATP is detectable in whole blood 40 s after bolus injection. Some of the pharmacological effects observed after ATP administration in humans are believed to be due to the action of the degradation products of ATP, especially adenosine and inosine.

Cardiology
Adenosine has established clinical application in cardiology as an anti-arrhythmic agent. It is administered, usually as an i.v. bolus at doses up to 15 mg, to restore sinus rhythm in patients with supraventricular tachycardia and for the diagnosis of broad and narrow complex tachycardia.

I.V. or intracoronary adenosine is also used to achieve maximal hyperaemia of the coronary microcirculation in the evaluation of the significance of coronary stenosis. The use of adenosine in ischaemia and reperfusion has gained increasing interest over the last decade. Adenosine exerts cardioprotective effects during myocardial ischaemia and reperfusion. Exogenous administration of adenosine prior to zero-flow ischaemia has been shown to reduce infarct size and improve functional recovery. Exogenous administration during low-flow ischaemia can improve functional recovery and reduce cellular injury, thereby slowing ATP depletion and delaying ischaemic contracture. Nevertheless, because of its haemodynamic side-effects and short half-life in blood (0.5–1.5 s), adenosine is not routinely used for the treatment of acute myocardial ischaemia. As adenosine produces coronary vasodilatation with only minor effects on the systemic circulation, its use for the prevention of early occlusion of coronary artery bypass grafts has been suggested.

A new application for adenosine is its use in myocardial contrast echo cardiography.

Control of arterial pressure
ATP and adenosine have been used experimentally for a number of years to induce hypotension during anaesthesia and surgery in patients. In 1951, Davies and colleagues demonstrated that an i.v. or intra-arterial bolus injection of ATP 40 mg induced a moderate fall in arterial pressure without change in heart rate. The haemodynamic effects of ATP and adenosine have been investigated in >150 patients undergoing different types of surgery, including oral.
orthopaedic, abdominal aortic aneurysm and cerebral aneurysm.

I.V. infusion of ATP or adenosine 50–350 µg kg\(^{-1}\) min\(^{-1}\) induced dose-related reductions of 20–43% in arterial pressure. A major decrease in systemic vascular resistance (36–67%) and an increase in cardiac output (14–42%), but only a small increase in heart rate (3–16%), occurred at higher doses. Haemodynamic values returned to their baseline immediately after stopping the infusion. No observations of tachyphylaxis and rebound hypertension have been reported. Other studies have shown no change in arterial pressure during infusion of adenosine 80 µg kg\(^{-1}\) min\(^{-1}\) in patients undergoing abdominal, breast or shoulder surgery. This is probably due to differences in dosing of adenosine.

ATP and adenosine (150–300 µg kg\(^{-1}\) min\(^{-1}\) i.v.) have been used successfully to antagonize the vasoconstrictive actions of norepinephrine and/or sympathetic nerve stimulation.

**Pain reduction**

Adenosine plays an important role in the perception of pain in the central and peripheral nervous system. The spinal cord contains adenosine A1, A2A, A2B and A3 receptors. The A1 receptor plays a key role in spinal antinoceception, whereas the functions of the A2A, A2B and A3 receptors are not clearly defined. At peripheral sites, A2A and A3 receptors mediate pain transmission, whereas the A1 receptor seems to play a central role in antinoceception.

Raising extracellular levels of adenosine through inhibition of adenosine kinase in animal models induced an analgesic effect. Unlike the direct effects of adenosine receptor agonists, use of adenosine kinase inhibitors does not have an effect on cardiovascular functions. The effects of adenosine are related to peripheral sensitization/activation of nociceptive afferents and influence the need for anaesthetics.

Adenosine induces release of neurotransmitters in spinal antinoceception, acting both pre- and post-synaptically. Pre-synaptically it reduces neurotransmitter release, and post-synaptically it hyperpolarizes the spinal cord neurones by interaction with ATP-sensitive K\(^+\) channels to increase the conductance.

**Anaesthesia and acute pain**

Several double-blind placebo-controlled cross-over studies in healthy human subjects have shown pain-reducing effects of i.v. adenosine infusion at doses of 50–70 µg kg\(^{-1}\) min\(^{-1}\). In addition, the effectiveness of adenosine in reducing ischaemic pain (70 µg kg\(^{-1}\) min\(^{-1}\) i.v. for 30 min) is comparable to morphine (20 µg kg\(^{-1}\) min\(^{-1}\) i.v. for 5 min) or ketamine (20 µg kg\(^{-1}\) min\(^{-1}\) i.v. for 5 min). Furthermore, adenosine given in combination with morphine or ketamine has an additive effect on pain reduction. In two double-blind randomized trials in patients undergoing breast surgery (75 patients) and gynaecological abdominal surgery (43 patients), systemic adenosine infusion (80 µg kg\(^{-1}\) min\(^{-1}\) i.v.) significantly reduced perioperative isoflurane requirements and postoperative pain. In addition, in both studies, the need for opioids was reduced by approximately 25% in the adenosine group during the first postoperative 24 h. A recent study suggested that adenosine infusion during general anaesthesia for surgery provided good recovery from anaesthesia associated with pronounced and sustained postoperative pain relief. In this study, adenosine (50–500 µg kg\(^{-1}\) min\(^{-1}\)) during surgery induced pain relief, reduced opioid requirements and attenuated side-effects such as protracted sedation, cardio-respiratory instability, nausea and vomiting during the postoperative recovery period. In all these aspects, adenosine was superior to remifentanil (0.05–0.5 µg kg\(^{-1}\) min\(^{-1}\)). These results suggest that adenosine acts by inhibiting nociceptive transmission. This may be mediated by central A1-receptor-mediated antinociception, and inhibition of peripheral inflammatory processes via A2A and possibly A3 receptors. It is possible that both central and peripheral mechanisms are involved. This is in line with the finding that, during surgical tissue injury and subsequent inflammatory processes, inhibition of both central and peripheral sensitization is necessary to prevent postoperative pain.

**Chronic pain**

Several reports have provided evidence that low doses of adenosine (50 µg kg\(^{-1}\) min\(^{-1}\)) alleviate neuropathic pain, hyperalgesia and allodynia without inducing other pain symptoms. Adenosine, infused for 45–60 min, induced improvement of spontaneous or evoked pain in six of seven patients with peripheral neuropathic pain for periods lasting from 6 h to 4 days. This positive finding was unexpected, as adenosine is eliminated from the blood within 1–2 min. The effects of adenosine on central hyperexcitability persist longer than the direct action of adenosine on the receptors. A role for adenosine in analgesia is further supported by the observation of reduced adenosine levels in the blood and cerebrospinal fluid of patients with neuropathic pain compared with patients who have nervous system lesions but no pain.

It is known that adenosine acts both pre- and post-synaptically. Pre-synaptically it reduces neurotransmitter release, and post-synaptically it hyperpolarizes the spinal cord neurones by interaction with ATP-sensitive K\(^+\) channels to increase the conductance.
Activation of P2X3 receptors contributes to the expression of chronic inflammatory and neuropathic pain states. After nerve injury, P2X3 receptors are upregulated in dorsal root ganglia. Activation of P2X3 receptors contributes to the expression of P2X3 ligand-gated cation channels mediate the excitatory effects of ATP on sensory neurones. After nerve injury, P2X3 receptors are upregulated in dorsal root ganglia. Activation of P2X3 receptors contributes to the expression of chronic inflammatory and neuropathic pain states. ATP acts via P2X3-containing channels as a nociceptive neurotransmitter. Unlike P2X receptors, activation of UTP-sensitive P2Y receptors produces inhibitory effects on spinal pain transmission.

Overall, these data demonstrate that activation of P2X3 receptors contributes to the expression of chronic inflammatory and neuropathic pain states. It is possible that relief from these forms of chronic pain might be achieved by selective blockade of the expression of P2X3 receptors.

Sepsis and shock

Shock and associated multiple organ failure is still a major cause of death in critically ill patients. A common feature of shock is an inadequate circulation leading to diminished perfusion, hypoxia and tissue injury. The resuscitation period after shock is also associated with development of tissue injury and loss of organ function. Severe sepsis and septic shock still have a high mortality, and current therapies have not had a substantial effect on survival. The recent development of recombinant activated protein C may hold more promise; however, the need for better medication remains urgent.

In the early 1980s, Chaudry and colleagues reported beneficial effects of ATP–MgCl2 in the treatment of haemorrhagic shock. Although this was originally attributed to restoration of energy supplies, the total amount of ATP–MgCl2 applied was minimal in relation to total body stores of ATP. The discovery of purinergic receptors provided a scientific explanation for the beneficial effects of ATP–MgCl2, such as improvement of blood flow, microcirculation, energy balance, and cellular and mitochondrial functions. However, some of the effects of ATP–MgCl2 infusion described by Chaudry and colleagues may be due to magnesium. Magnesium is a cofactor for more than 300 enzymes, some of which catalyse oxidative phosphorylation, activating energy storage and metabolizing ATP. Furthermore, magnesium is involved in the regulation of cell membrane permeability and arteriolar tone, and enhances the binding of agonists to P1 receptors. Paskitti and Reid reported that vanadate may play a role in the ATP–MgCl2 effect, as the ATP used was derived from equine muscle and not from bacterial sources and therefore contained trace amounts of vanadate. Both ATP and vanadate given alone had a smaller but still significant effect.

Chaudry and colleagues reported that ATP–MgCl2 infusion was beneficial for the survival of rats and mini-pigs after haemorrhagic shock, sepsis and peritonitis. ATP–MgCl2 accelerated the recovery of renal function after ischaemia. However, bolus administration of ATP–MgCl2 had profound circulatory effects, and was suggested as a cause of shock.

The short-lived response to i.v. ATP–MgCl2 infusion in a clinically relevant hypoxic–hypotensive rat model confirmed the necessity of prolonged continuous infusion of ATP–MgCl2. In vivo animal studies indicate that infusion of ATP–MgCl2 after haemorrhagic shock has a favourable effect on survival. Other studies suggest that ATP and adenosine have protective effects on tissue injury following reperfusion after a period of ischaemia. The beneficial effect of ATP–MgCl2 in shock could be due to provision of energy directly to tissue with low levels of ATP. ATP–MgCl2 has been shown to improve the function of rat kidney, rat liver, dog heart, rabbit lung and rat gut after a period of ischaemia. The use of i.m. ATP–MgCl2 was also protective in rats with burns.

Another animal study indicated that administration of ATP–MgCl2 early after the onset of sepsis attenuated the impaired endothelium-dependent vascular relaxation. In this way, ATP may be effective in maintaining endothelial cell function during the hyperdynamic stage of sepsis. A mouse model of sepsis was used to investigate the influence of ATP–MgCl2 infusion on high-energy phosphate stores and immune function in lymphocytes. Treatment with ATP–MgCl2 at the onset of sepsis significantly increased lymphocyte ATP levels and the proliferation response to mitogenic stimuli. Moreover, improved lymphocyte function in this group correlated with a significant increase in overall survival of the animals. It was suggested that decreased lymphocyte ATP levels might be the cause of defective lymphocyte proliferation capacity in late sepsis. In a porcine model, it was shown that ATP–MgCl2 normalized the lipopolysaccharide-induced rise in the ileal–mucosal PCO2 gap and attenuated hepatic lactate clearance.

ATP production by mitochondrial oxidative phosphorylation accounts for more than 90% of total oxygen consumption. Brealey and colleagues postulated that mitochondrial dysfunction results in organ failure, possibly because of production of nitric oxide which is known to inhibit mitochondrial respiration in vitro and is produced in excess in sepsis. In a group of 28 critically ill septic patients, these authors showed that skeletal muscle concentrations of ATP were significantly lower in the12 patients who subsequently died (7.6 nmol mg−1 dry weight) compared with both the 16 patients who survived (15.8 nmol mg−1) and controls (12.5 nmol mg−1).

In septic patients, an association was found between nitric oxide overproduction, antioxidant depletion, mitochondrial dysfunction and decreased intracellular ATP concentrations. Addition of extracellular ATP may replace this deficit. The repletion of intracellular ATP pools during ATP infusion in humans has been observed.
using $^{31}$P magnetic resonance spectroscopy in patients with cancer cachexia.27,55

In the light of these findings, studies to evaluate the use of ATP infusions in relation to sepsis have been proposed. A particular target is the treatment of impaired microcirculation where ATP or adenosine could provide a valuable alternative to the current use of vasopressor medication to increase arterial pressure.59 After restoring volume depletion, the combined ATP effects of vasodilation and increased cardiac output could be used to improve microcirculation and tissue perfusion, and to increase oxygen delivery/extraction.

Conclusion

Based on the evidence from both animal and clinical studies performed during the last 20 years, ATP could provide a valuable addition to the therapeutic options in anaesthesia and intensive care medicine. In particular, its use in pain management, modulation of haemodynamics and treatment of shock seems promising. Further research is required, particularly on the issue of ATP–MgCl$_2$, to clarify the exact role of ATP, magnesium and the combined compound.

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References


11 Bouma MG, van den Wildenberg FA, Buurman WA. The anti-inflammatory potential of adenosine in ischemia-reperfusion injury: established and putative beneficial actions of a retaliatory metabolite. Shock 1997; 8: 313–20


16 Chaudry IH. Use of ATP following shock and ischemia. Ann NY Acad Sci 1990; 603: 330–41


26 Cronstein BN, Naime D, Firestein G. The antiinflammatory effects of an adenosine kinase inhibitor are mediated by adenosine. Arthritis Rheum 1995; 38: 1040–5


33 Filkins JP, Buchanan BJ. Protection against endotoxin shock and impaired glucose homeostasis with ATP. Circ Shock 1977; 4: 253–8
44 Hirasawa H, Chaudry IH, Baue AE. Improved hepatic function and survival with adenosine triphosphate-magnesium chloride after hepatic ischemia. Surgery 1978; 83: 655–62
45 Hirasawa H, Ohkawa M, Odaka M, Sato H. Improved survival, RES function, and ICG test with ATP–MgCl2 following hepatic ischemia. Surg Forum 1979; 30: 158–60
48 Jacobson KA, Jarvis MF, Williams M. Purine and pyrimidine (P2) receptors as drug targets. J Med Chem 2002; 45: 4073–97
60 Mulvagh SL. Advances in myocardial contrast echocardiography and the role of adenosine stress. Am J Cardiol 2004; 94: 12–17
63 Ohkawa M, Clemens MG, Chaudry IH. Studies on the mechanism of beneficial effects of ATP–MgCl2 following hepatic ischemia. Am J Physiol 1983; 244: R695–702
64 Okada M, Kaneko S. Pharmacological interactions between magnesium ion and adenosine on monoaminergic system in the central nervous system. Magnes Res 1998; 11: 289–305
77 Sawynok J. Adenosine receptor activation and nociception. *Eur J Pharmacol* 1998; 347: 1–11
78 Sawynok J. Reid A. Peripheral adenosine 5’-triphosphate enhances nociception in the formalin test via activation of a purinergic p2X receptor. *Eur J Pharmacol* 1997; 330: 115–21
100 Zaki MS, Burke JF, Trelstad RL. Protective effects of adenosine kinase inhibitor, relieves tactile allodynia via spinal sites of action in peripheral nerve injured rats. *Brain Res* 2001; 905: 104–10