

Adenosine A2a receptor agonists as regulators of inflammation: pharmacology and therapeutic opportunities

Silvana Morello
Rosalinda Sorrentino
Aldo Pinto

Department of Pharmaceutical
Sciences, Biomedical Section,
University of Salerno, Via Ponte don
Melillo, 84084 Fisciano, Salerno, Italy

Abstract: A2a receptor (A2aR) plays an important role in the regulation of inflammatory and immune responses. The activation of PKA-dependent and/or -independent pathways are responsible for the downmodulation of inflammatory networks and tissue injury. Based on promising recent studies, selective A2aR agonists are under clinical investigations for a wide range of disorders, such as ischemia-reperfusion injury, chronic inflammation, and infectious diseases. Nevertheless, further studies are required to improve our understanding in the ability of A2a receptor agonists to reduce tissue damage during inflammation. Characterization of A2aR-induced signaling pathways will be useful for the development of novel therapeutic strategies in inflammatory/immune diseases.

Keywords: adenosine, A2a receptor, A2a receptor agonists, inflammation

Introduction

Adenosine, endogenous ATP metabolite, is highly released during pathological conditions, such as hypoxia and ischemia.¹ Cell distress and tissue damage increase the release of adenosine 200-fold in the extracellular compartment compared to physiological conditions.¹

Adenosine can signal through four cell-surface receptors: A1R, A2aR, A2bR and A3R, all coupled to GTP-binding proteins.² The activation of the adenosine signaling pathways is strictly dependent on the extracellular concentration of the nucleoside. A1R and A2aR are activated by low levels of adenosine (0.01 to 1 μ M), whereas A2bR and A3R require higher amounts (>10 μ M).¹ Based on both their tissue/organ expression and on their cell density, adenosine receptors can play differential role(s), which can be ascribed to cyclic-AMP (cAMP)-dependent or independent signaling pathways. In this regard, since the four receptors can mediate different effects, it is of note that the activation of one receptor can lead to a signaling pathway that is opposed to the signaling induced by another adenosine receptor. For example, the activation of A1 and A3 receptors, G_{i/o}-coupled, leads to the reduction of cAMP levels, whereas the stimulation of A2a and A2b receptors, G_s-coupled, leads to the increase of cAMP.²

Among the different adenosine receptor subtypes, A2aR plays a crucial role in the regulation of inflammatory patterns.³⁻⁷ Many excellent recent reviews are available on the activity of A2aR agonists as potential anti-inflammatory and immunosuppressive agents.⁷⁻¹¹ Hence, because of the clinical interest in this receptor, many selective A2aR agonists, such as CGS21680 {2-[p-(2-carboxyethyl) phenylethylamino]-5'-N-ethyl-carboxamidoadenosine},¹² ATL146e {2-[p-(2-carboxyethyl)phenylethylamino]-5'-N-ethyl-carboxamidoadenosine},¹³ or ATL313, all of which are orally active, have

Correspondence: Silvana Morello
Department of Pharmaceutical Sciences,
Biomedical Section, University of Salerno,
Via Ponte don Melillo, 84084, Fisciano
(SA), Italy
Tel +39-089-969454
Email morello.silvana@gmail.com
or smorello@unisa.it

been synthesized, as have the A2aR antagonists ZM241385 (4-{2-[7-amino-2-(2-furyl) (1, 2, 4) triazolo (2,3-a) (1, 3, 5) triazin-5-ylamino] ethyl}-phenol) and various 1,2,4-triazolo [1,5-c] pyrimidines derivatives such as the highly selective SCH 420814.¹⁴ ATL146e and ATL313, A2aR agonists, are more selective than CGS21680 and therapeutically more interesting, with lower side effects.¹⁵

A2a receptor signaling transduction and regulation of inflammation by A2a receptor agonists

A2a receptor is coupled to a G_s protein. Its stimulation leads to the accumulation of intracellular cAMP levels,¹⁶ which is a key regulator of immune and inflammatory responses. cAMP signals mainly through the protein kinase cAMP-dependent (PKA) that activates the nuclear substrate cAMP responsive element-binding protein (CREB) by phosphorylation at the level of Ser-133.¹⁷ This latter binds to the nuclear co-factor CBP and to p300, and the complex in turn regulates the expression of many genes by binding to cAMP responsive elements in their promoter regions.¹⁷ Importantly, CREB can indirectly regulate the transcription of many inflammatory genes competing with nuclear factor- κ B (NF- κ B)/p65 for CBP (Figure 1).¹⁸ The latter is probably one of the major mechanisms by which A2aR stimulation inhibits the transcriptional activity of NF- κ B in a PKA/CREB-dependent manner, subsequently suppressing the expression of pro-inflammatory cytokines, such as tumour necrosis factor (TNF- α).¹⁹ However, a very recent paper showed that adenosine could interfere with NF- κ B dependent inflammatory pathways, assuming that small ubiquitin-like modifier 1 (SUMO-1) blocked I κ B α in a sumoylated form, avoiding its phosphorylation/degradation, and thus NF- κ B nuclear translocation.²⁰ Presumably this effect was also associated with increased intracellular cAMP levels. However, this latter paper referred to the general adenosine receptors agonist NECA and not to A2aR activation, implying further studies on this concept.

cAMP can also activate other substrates, such as EPAC 1, exchange protein directly activated by cAMP, altering pro-inflammatory genes expression (Figure 1).²¹ In this context, Sands and collaborators demonstrated that following A2aR stimulation, the accumulation of cAMP and the activation of EPAC1 in vascular endothelial cells could suppress pro-inflammatory cytokines-induced Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) pathways, effect related to the suppressor of cytokine signaling-3 (SOCS-3).^{22,23} In the same work the authors observed that the upregulation of SOCS-3 by cAMP could also occur

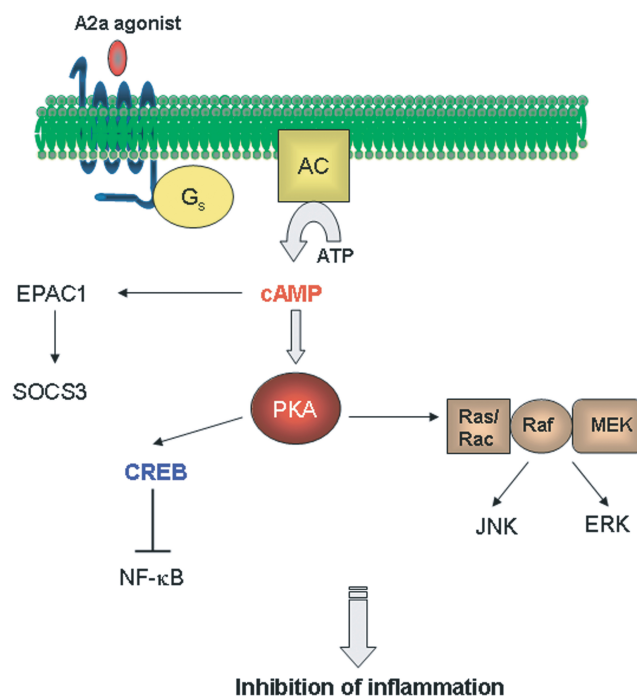


Figure 1. A2a receptor signaling pathways. A2a receptor is coupled to a G_s protein. Its activation leads to the accumulation of intracellular levels of cAMP generated by the enzyme adenylyl cyclase (AC). This latter triggers the activation of protein kinase cAMP-dependent (PKA) and subsequently activation of cAMP responsive element-binding protein (CREB), which in turn inhibits NF- κ B. Alternative cAMP-mediated pathway(s) have been also investigated, such as modulation of MAPK signaling pathway (JNK, ERK). A2a receptor stimulation may also induce SOCS-3 expression through EPAC-1 in a cAMP-dependent manner.

following ERKs pathway activation. Recently, it has been reported that the induction of SOCS3 expression in response to cAMP depends on the activation of transcription factors CCAAT/enhancer-binding proteins (C/EBPs) by EPAC1.²⁴ These latter data provide another potential mechanism by which activators of adenylyl cyclase, such as A2aR, could modulate the expression of different genes involved in the regulation of inflammatory responses that may occur in a PKA-independent manner.

A2aR expression can be modulated by inflammatory pathways. The expression of A2aR was induced by lipopolysaccharide (LPS) or by inflammatory cytokines such as TNF- α and IL-1 β because of the presence of putative NF- κ B consensus sites in its promoter region.^{25–28} Hence, we could speculate that during inflammatory conditions the overexpression of A2aR by inflammatory cytokines could imply an endogenous negative feedback, avoiding devastating effects.

A2aR essentially suppress inflammatory and immune responses by reducing production of many pro-inflammatory cytokines from different cell types. One of the first pieces of evidence on this matter was shown by Sullivan et al who

demonstrated that CGS21680 inhibits TNF- α production from monocytes and macrophages in response to microbial products, such as endotoxin.²⁹ CGS21680-mediated effects on accumulation of pro-inflammatory cytokines, such as TNF- α and IL-12, in macrophages activated via Toll-like receptor (TLR) agonists or by cytokines, is related to cAMP-mediated inhibition of NF- κ B, via inhibition of I κ B phosphorylation.³⁰ However, the molecular mechanism of this inhibition appears to be cell type-specific, since in vascular endothelial cells degradation of I κ B proteins is unaffected by A2a receptor expression.³¹ However, further investigations on the precise mechanism(s) of how A2aR negatively interferes with NF- κ B signaling pathway are still needed.

It is important to note that although it has been strongly supposed that A2aR is the main adenosine receptor subtype that suppresses pro-inflammatory cytokines production, other adenosine receptors may also be involved, such as A2bR.³² In this regard, Yang and collaborators showed that A2bR activation negatively regulates inflammatory responses induced by endotoxin in macrophages.³³ Consistent with these results, a very recent paper reported that A2bR is the predominant immunoregulatory receptor in murine dendritic cells (DCs) stimulated with LPS, suggesting that adenosine may regulate CD4⁺ T cell responses, impairing DCs maturation via A2bR.³⁴

Extracellular adenosine inhibits the activity of T cells because A2aR triggers the accumulation of intracellular cAMP.³⁵ The second messenger cAMP regulates the immune responses activated through the T-cell receptor (TCR), inhibiting Src-family kinase signaling by PKA-mediated phosphorylation and activation of C-terminal Src kinase (Csk).³⁶ Therefore, A2aR activation leads to the inhibition of TCR-triggered effector functions, including proliferation, expansion and secretion of important cytokines such as interferon (IFN)- γ , TNF- α , IL-4 and IL-2 via cAMP/PKA-dependent pathways. This phenomenon was described for both naïve CD4⁺ T cells and polarized Th1 and Th2 cells.^{37–39} Furthermore, the inhibitory effects of A2aR agonists on T cells and antigen presenting cells (APCs) are also ascribed to the inhibition of activation markers CD25 and CD40L expression and induction of programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) expression on T cells.⁴⁰

In addition to its effects on lymphocyte function, A2aR stimulation also modulates neutrophil functions and therefore inflammatory damage to the endothelium. Indeed, A2aR agonists are the most potent agents limiting the inflammatory activities of neutrophils,^{41–43} such as the production of reactive oxygen species, phagocytosis, adhesion molecules

and cytokine release. Moreover, A2aR activation inhibits leukotrienes and platelet-activating factor (PAF) release from neutrophils.^{44–46} CGS21680 stimulates cyclooxygenase-2 expression in neutrophils and thus increases the capacity of these cells to produce prostaglandins E2, that have potent anti-inflammatory activities on leukocytes and other inflammatory cells.^{47–50}

Interestingly, in human neutrophils stimulated with known inflammatory agents, it has been demonstrated very recently that CGS21680 and other c-AMP-elevating compounds could modulate the expression profile of many genes, encoding transcription factors, enzymes and regulatory proteins, as well as cytokines and chemokines involved in molecular signaling pathways associated with the resolution of inflammation.⁵¹

From experimental evidences to therapeutic opportunities for A2aR agonists

Based on the research reported above, the clinical interest in A2aR agonists as modulator of inflammatory and immune responses has increased strongly, especially for some pathological conditions, such as heart, liver, kidney, or spinal cord ischemia-reperfusion injury or chronic inflammatory conditions of the respiratory system or infectious diseases.

The selective A2a receptor agonist ATL146e has been tested in mice after reperfusion of the coronary artery⁵² and in mice lacking T cells after ischemia-reperfusion.⁵³ In both experimental conditions the beneficial response following A2aR activation on CD4⁺ T cells, in terms of reduction of tissue damage, depends on the modulation of T lymphocytes accumulation, neutrophils recruitment and IFN- γ release into the infarcted area.

Selective A2aR agonists are actually under investigation as pharmacological stress agents (Phase III studies) (regadenoson and binodenoson), providing selective coronary vasodilatation compared to adenosine, which is currently used for myocardial perfusion imaging procedures, but unfortunately associated with a high incidence of side effects.⁵⁴

Similar effects were observed in a condition of ischemia-reperfusion injury of the liver or kidney. The protective effects of CGS21680 and ATL146e on ischemia-reperfusion damage in the liver or in the kidney depend on the inhibition of cytokines production by CD4⁺ T cells, as IFN- γ , and neutrophils infiltration.^{55–59} Adoptive transfer studies implying CD4⁺ T cells from mice lacking A2aR supported that the protective role of A2aR, stimulated with ATL146e,

was CD4+ T cell-dependent^{56,58} Furthermore, NKT cells were also essential since NKT-deficient animals or animals with A2aR knocked down only on NKT were not protected from ischemia-reperfusion liver injury.⁵⁹ These studies suggest overall that bone marrow-derived cells are the primary cellular targets through which A2aR activation affords protection from ischemia-reperfusion injury.

Another potential therapeutic application for A2aR agonists is in the prevention and treatment of diabetic complications. Indeed, similar to the effects observed in acute renal ischemia-reperfusion injury, it has been shown that ATL146e attenuates inflammation and renal injury associated to diabetic nephropathy.⁶⁰ Interestingly, topical application of the selective A2aR agonist MRE0094 is under clinical investigation for the treatment of poorly healing diabetic foot ulcers. A large body of evidence has demonstrated that stimulation of A2aR, expressed on cells involved in wound healing (fibroblasts, endothelial cells, inflammatory cells) promotes extracellular matrix production and vessel formation.^{61–63} Very recently, A2aR was demonstrated to also play a critical role for the proliferation and differentiation of bone marrow cells, essential for wound healing, tissue repair and organ regeneration.⁶⁴

The anti-inflammatory actions of A2aR agonists on lung inflammation might be based on the same mechanism described above. In this regard, several lines of evidence suggest that A2aR may represent an attractive target for lung inflammation treatment.⁶⁵ For example, CGS21680 administration attenuated lung inflammation by inhibition of neutrophil, macrophage, eosinophil and lymphocyte infiltration, and cytokine levels.^{66,67} Mice lacking A2aR show enhanced lung inflammation in response to inflammatory stimuli.⁶⁸ In addition to potent anti-inflammatory actions in lung inflammation, CGS21680 may also reduce lung injury caused by an episode of trauma and hemorrhagic shock.⁶⁹ The therapeutic benefit of A2aR agonists in preventing tissue damage and acute respiratory distress caused by oxygen therapy should be noted.⁷⁰ However, CGS21680 administration for the treatment of lung inflammation causes important side effects on blood pressure.⁶⁶ A new A2aR agonist, GW328267,⁷¹ is in clinical trial for the treatment of asthma induced by allergens⁷² and allergic rhinitis,⁷³ although the utility of this agonist needs further investigation because of its increased side effects. Of note, a very recent selective A2aR agonist, UK371,104, intra-tracheally administered, revealed beneficial effects on lung inflammation without any side effect on blood pressure compared to CGS21680.⁷⁴ Indeed, analogues of UK371,104, such as UK432,097, are currently in phase II trials for chronic obstructive pulmonary disease.⁷⁴

Another beneficial effect for the A2aR agonist ATL146e, was for the acute spinal cord injury treatment.^{75,76} The A2aR agonist administration can attenuate functional injury following ischemic spinal cord. However, it is important to point out that the administration of A2a agonists did not prove of therapeutic benefit since the already altered healthy conditions of spinal cord injured patients. Hence, it was postulated that A2aR agonists could be employed only prophylactically.⁷⁶

The A2aR agonist ATL146e is of increasing interest for the treatment of sepsis.⁷⁷ Moore and collaborators reported that ATL313, highly selective for A2aR, improves the survival of mice challenged with a Gram-negative (*Escherichia coli*) or Gram-positive (*Staphylococcus aureus*) pathogens or purified LPS, by modulating the serum level of multiple cytokines.⁷⁸ Although further investigations are needed to explore the effects of A2aR agonists in sepsis, the authors however suggest the possible clinical utility of ATL313. In contrast, in another model of sepsis induced by cecal ligation and puncture, the genetic absence or the pharmacological inactivation of A2aR increased mice survival rate and improved bacterial clearance, as a resultant of increased immune responsiveness;⁷⁹ the authors concluded that A2aR antagonists could be beneficial in a septic condition. To explain this discrepancy with other findings that describe beneficial effects for A2aR agonists, the authors suggested a differential role of A2aR for bacterial survival in an acute inflammatory condition, such as sepsis. However, further studies are needed to clarify the role of A2aR in infectious disease, looking at the involvement of A2aR in bacterial growth compared with the host immune defence.

The therapeutic utility of A2aR agonists was also proved in bacterial meningitides, the activation of which led to decreased cytokine and reactive oxygen species production, degranulation of polymorphonuclear leukocytes and neutrophil-induced damage.⁸⁰

Finally, early preclinical studies have demonstrated that A2aR activation attenuates stress- and aspirin-induced gastric injury.^{81,82} A very recent paper showed that A2aR activation by means of ATL313, orally active, inhibits gastric injury induced by indomethacin.⁸³ Gastric protection is correlated with reduction of neutrophils infiltration into the gastric mucosal tissue by inhibiting the production of pro-inflammatory cytokines in the gastric mucosa. In this way, oral administration of ATL313 may be clinically useful in reducing gastric mucosal damage induced by nonsteroidal anti-inflammatory drugs.

Conclusions

In conclusion, increasing evidence supports the essential role of A2aR in the regulation of inflammatory and immune responses.

A2a ligands were shown to resolve inflammation and reduce tissue injury in a cAMP-dependent manner. However, for inflammatory patterns further studies will be necessary to provide a better understanding of how all four adenosine receptors are expressed and especially their tissue-specific activity and/or the possible cross-talk among adenosine receptor-mediated signaling pathways.

Thus, characterization of these signaling pathways is likely critical for the development of therapeutic strategies in inflammatory/immune diseases.

Disclosure

The authors declare no conflicts of interest.

References

- Fredholm BB Adenosine, an endogenous distress signal, modulates tissue damage and repair. *Cell Death Differ.* 2007;14:1315–1323.
- Fredholm BB, IJzerman AP, Jacobson KA, et al. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol Rev.* 2001;53(4):527–552.
- Cronstein BN, Kramer SB, Weissmann G, et al. Adenosine: a physiological modulator of superoxide anion generation by human neutrophils. *J Exp Med.* 1983;158:1160–1177.
- Cronstein BN, Rosenstein ED, Kramer SB, et al. Adenosine: a physiological modulator of superoxide anion generation by human neutrophils. Adenosine acts via an A2 receptor on human neutrophils. *J Immunol.* 1985; 135:1366–1371.
- Linden J. Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. *Annu Rev Pharmacol Toxicol.* 2001;41:775–787.
- Ohta A, Sitkovsky M. Role of G-protein-coupled adenosine receptors in down-regulation of inflammation and protection from tissue damage. *Nature.* 2001;414:916–920.
- Sitovsky MV. Use of the A2a adenosine receptor as physiological immunosuppressor and to engineer inflammation *in vivo*. *Biochem Pharmacol.* 2003;65:493–501.
- Sitovsky MV, Lukashev D, Apasov S, et al. Physiological control of immune response and inflammatory tissue damage by hypoxia-inducible factors and adenosine A2a receptors. *Annu Rev Immunol.* 2004;22:657–682.
- Lappas CM, Sullivan GW, Linden J. Adenosine A2A agonists in development for the treatment of inflammation. *Expert Opin Investig Drugs.* 2005;14:797–806.
- Palmer TM, Trevethick MA. Suppression of inflammatory and immune responses by the A2a adenosine receptor: an introduction. *Br J Pharmacol.* 2008;153 Suppl 1:S27–S34.
- Haskó G, Pacher P. A2A receptors in inflammation and injury: lessons learned from transgenic animals. *J Leukoc Biol.* 2008;83(3): 447–455.
- Hutchinson AJ, Webb RL, Oei HH, et al. CGS21680, an A2 selective adenosine receptor agonist with preferential hypotensive activity. *J Pharmacol Exp Ther.* 1989;251:47–55.
- Rieger JM, Brown ML, Sullivan GW, et al. Design, synthesis, and evaluation of novel A2A adenosine receptor agonists. *J Med Chem.* 2001;44:531–539.
- Neustadt BR, Hao J, Lindo N, et al. Potent, selective, and orally active adenosine A2A receptor antagonists: Arylpiperazine derivatives of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines. *Bioorg Med Chem Lett.* 2007;1376–1380.
- Ledent C, Vangeois JM, Schiffmann SN, et al. Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine receptor A2a. *Nature.* 1997;338:674–678.
- Fredholm BB, Chern Y, Franco R, et al. Aspects of the general biology of adenosine A_{2A} signalling. *Prog Neurobiol.* 2007;83:263–276.
- Mayr B, Montminy M. Transcriptional regulation by the phosphorylation-dependent factor CREB. *Nat Rev Mol Cell Biol.* 2001;2:599–609.
- Lin MC, Almus-Jacobs F, Chen HH, et al. Shear stress induction of the tissue factor gene. *J Clin Invest.* 1997;99:737–744.
- Bshesh K, Zhao B, Spight D, et al. The A_{2A} receptor mediates an endogenous regulatory pathway of cytokine expression in THP-1 cells. *J Leukoc Biol.* 2002;72:1027–1036.
- Liu Q, Li J, Khoury J, et al. Adenosine signaling mediates SUMO-1 modification of I {kappa} B {alpha} during hypoxia and reoxygenation. *J Biol Chem.* 2009;284 (20):13686–13695.
- Kawasaki H, Springett GM, Monchizuki N, et al. A family of cAMP-binding proteins that directly activate Rap1. *Science.* 1998;282:2275–2279.
- Sands WA, Woolson HD, Milne GR, et al. Exchange protein activated by cyclic AMP (Epac)-mediated induction of suppressor of cytokine signalling 3 (SOCS-3) in vascular endothelial cells. *Mol Cell Biol.* 2006;26:6333–6346.
- Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signaling and immune regulation. *Nat Rev Immunol.* 2007;7:454–465.
- Yarwood SJ, Borland G, Sands WA, et al. Identification of CCAAT/enhancer-binding proteins as exchange protein activated transcription factors that mediate the induction of the SOCS-3 gene. *J Biol Chem.* 2008;283:6843–6853.
- Khoa ND, Montesinos MC, Reiss AB, et al. Inflammatory cytokines regulate function and expression of adenosine A_{2A} receptors in human monocytic THP-1 cells. *J Immunol.* 2001;167:4026–4032.
- Murphee LJ, Sullivan GW, Marshall MA, et al. Lipopolysaccharide rapidly modify adenosine receptor transcripts in murine and human macrophages: role of NF-κB in A_{2A} adenosine receptor induction. *Biochem J.* 2005;391:575–580.
- Capecchi PL, Camurri A, Pompella G, et al. Up-regulation of A2A adenosine receptor expression by TNF-α in PBMC of patients with CHF: a regulatory mechanism of inflammation. *J Card Fail.* 2005; 11(1):67–73.
- Morello S, Ito K, Yamamura S, et al. IL-1β and TNF-α regulation of the adenosine receptor (A2A) expression: differential requirement for NF-κB binding to the proximal promoter. *J Immunol.* 2006;177 (10):7173–7183.
- Sullivan GW, Carper HT, Mandell GL. The specific type IV phosphodiesterase inhibitor rolipram combined with adenosine reduces tumor necrosis factor-α-primed neutrophil oxidative activity. *Int J Immunopharmacol.* 1995;17(10):793–803.
- Haskó G, Pacher P, Deitch EA, et al. Shaping of monocyte and macrophage function by adenosine receptors. *Pharmacol Ther.* 2007;113:264–275.
- Sands WA, Martin AF, Strong EW, et al. Specific inhibition of nuclear factor-κB-dependent inflammatory responses by cell type-specific mechanisms upon A2A adenosine receptor gene transfer. *Mol Pharmacol.* 2004;66(5):1147–1159.
- Kreckler LM, Wan TC, Ge ZD, et al. Adenosine inhibits tumour necrosis factor-α release from mouse peritoneal macrophages via A2A and A2B but not the A3 adenosine receptors. *J Exp Pharmacol Ther.* 2006;317(1):172–180.
- Yang D, Zhang Y, Nguyen HG, et al. The A2b adenosine receptor protects against inflammation and excessive vascular adhesion. *J Clin Invest.* 2006;116:1913–1923.
- Wilson JM, Ross WG, Agbai ON, et al. The A2A adenosine receptor impairs the maturation and immunogenicity of dendritic cells. *J Immunol.* 2009;182:4616–4623.

35. Sitovsky MV, Lukashev D. Regulation of immune cells by local-tissue oxygen tension: HIF1 alpha and adenosine receptors. *Nat Rev Immunol*. 2005;5(9):712–721.
36. Tasken K, Stokka AJ. The molecular machinery for cAMP-dependent immunomodulation in T-cells. *Biochem Soc Trans*. 2006;34:476–479.
37. Naganuma M, Wiznerowicz EB, Lappas CM, et al. Cutting Edge: critical role for A_{2A} adenosine receptors in the T cell-mediated regulation of colitis. *J Immunol*. 2006;177:2765–2769.
38. Lappas CM, Rieger JM, Linden J. A2A adenosine receptor induction inhibits IFN-g production in murine CD4+ T cells. *J Immunol*. 2005;174:1073–1080.
39. Csóka B, Himer L, Selmecey Z, et al. Adenosine A2A receptor activation inhibits T helper 1 and T helper 2 cell development and effector function. *FASEB J*. 2008;22(10):3491–3499.
40. Sevigny CP, Li L, Awad AS, et al. Activation of adenosine A2A receptors attenuates allograft rejection and alloantigen recognition. *J Immunol*. 2007;178:4240–4249.
41. Cronstein BN, Levin RI, Philips M, et al. Neutrophil adherence to endothelium is enhanced via adenosine A1 receptors and inhibited via adenosine A2 receptors. *J Immunol*. 1992;148:2201–2206.
42. Zhao ZQ, Sato H, Williams MW, et al. Adenosine A2-receptor activation inhibits neutrophil-mediated injury to coronary endothelium. *Am J Physiol*. 1996;271:H1456–H1464.
43. Sullivan GW, Lee DD, Ross WG, et al. Activation of A_{2A} adenosine receptors inhibits expression of alpha4/beta1 integrin (very late antigen-4) on-stimulated human neutrophils. *J Leukoc Biol*. 2004;75:127–134.
44. Flamand N, Boudreaux S, Picard S, et al. Adenosine, a potent natural suppressor of arachidonic acid release and leukotriene biosynthesis in human neutrophils. *Am J Crit Care Med*. 2000;161(2 Pt 2):S88–S94.
45. Krump E, Borgeat P. Kinetics of 5-lipoxygenase activation, arachidonic acid release, and leukotriene synthesis in human neutrophils: effects of granulocyte-macrophage colony-stimulating factor. *Adv Exp Med Biol*. 1999;447:107–115.
46. Krump E, Picard S, Mancini J, et al. Suppression of leukotriene B4 biosynthesis by endogenous adenosine in ligand-activated human neutrophils. *J Exp Med*. 1997;186(8):1401–1406.
47. Cadieux JS, Leclerc P, St-Onge M, et al. Potentiation of neutrophil cyclooxygenase-2 by adenosine: an early anti-inflammatory signal. *J Cell Sci*. 2005;118 (7):1437–1447.
48. Flamand N, Surette ME, Picard S, et al. Cyclic AMP-mediated inhibition of 5-lipoxygenase translocation and leukotriene biosynthesis in human neutrophils. *Mol Pharmacol*. 2002;62(2):250–256.
49. Pouliot M, Fiset ME, Massé N, et al. Adenosine up-regulates cyclooxygenase-2 in human granulocytes: impact of the balance of eicosanoid generation. *J Immunol*. 2002;169 (9):5279–5286.
50. McColl SR, St-Onge M, Dussalt AA, et al. Immunomodulatory impact of the A2A adenosine receptor on the profile of chemokine produced by neutrophils. *FASEB J*. 2006;20(1):187–189.
51. St-Onge M, Dumas A, Michaud A, et al. Impact of anti-inflammatory agents on the gene expression profile of stimulated human neutrophils: unravelling endogenous resolution pathways. *Plos ONE*. 2009;4(3):e4902.
52. Yang Z, Day YJ, Toufektsian MC, et al. Infarct-sparing effect of A2A-adenosine receptor activation is due primarily to its action on lymphocytes. *Circulation*. 2005;111(17):2190–2197.
53. Yang Z, Day YJ, Toufektsian MC, et al. Myocardial infarct-sparing effect of adenosine A2A receptor activation is due to its action on CD4+ T lymphocytes. *Circulation*. 2006;114(19):2056–2064.
54. Cerqueira MD. The future of pharmacologic stress: selective A2a adenosine receptor agonists. *Am J Cardiol*. 2004;94:33D–40D.
55. Odashima M, Otaka M, Jin M, et al. A selective adenosine A2A receptor agonist, ATL-146e, prevents concanavalin A-induced acute liver injury in mice. *Biochem Biophys Res Commun*. 2006;347(4):949–954.
56. Day YJ, Huang L, McDuffie MJ, et al. Renal protection from ischemia mediated by A2A adenosine receptors on bone marrow-derived cells. *J Clin Invest*. 2003;112(6):883–891.
57. Day YJ, Li Y, Rieger JM, et al. A2A adenosine receptors on bone marrow-derived cells protect liver from ischemia-reperfusion injury. *J Immunol*. 2005;174(8):5040–5046.
58. Day YJ, Huang L, Ye H, et al. Renal ischemia-reperfusion injury and adenosine 2A receptor-mediated tissue protection: the role of CD4+ T cells and IFN-gamma. *J Immunol*. 2006;176(5):3108–3114.
59. Lappas CM, Day YJ, Marshall MA, et al. Adenosine A2A receptor activation reduces hepatic ischemia reperfusion injury by inhibiting CD1d-dependent NKT cell activation. *J Exp Med*. 2006;203(12):2639–2648.
60. Awad AS, Huang L, Ye H, et al. Adenosine A2A receptor activation attenuates inflammation and injury in diabetic nephropathy. *Am J Renal Physiol*. 2006;290:F828–F837.
61. Montesinos MC, Gadangi P, Longaker M, et al. Wound healing is accelerated by agonists of adenosine A2 (G alpha s-linked) receptors. *J Exp Med*. 1997;186:1615–1620.
62. Montesinos M, Chen JF, Desai A, et al. Adenosine promotes wound healing and mediates angiogenesis in response to tissue injury via occupancy of A2A receptors. *Am J Pathol*. 2002;160:2009–2018.
63. Victor-Vega C, Desai A, Montesinos M, et al. Adenosine A2A agonists promote more rapid wound healing than recombinant human platelet derived growth factor (PDGF). *Inflammation*. 2002;26:19–24.
64. Katebi M, Soleimani M, Cronstein BN. Adenosine A2A receptors play an active role in mouse bone marrow-derived mesenchymal stem cell development. *J Leukoc Biol*. 2009;85(3):438–444.
65. Trevelthick MA, Mantell SJ, Stuart EF, et al. Treating lung inflammation with agonists of the adenosine A2A receptor: promises, problems and potential solutions. *Br J Pharmacol*. 2008;155(4):463–474.
66. Fozard JR, Ellis KM, Villela Dantas MF, et al. Effect of CGS21680, a selective A_{2A}AR agonist, on allergic airways inflammation in the rat. *Br J Pharmacol*. 2002;438:183–188.
67. Bonneau O, Wyss D, Ferretti S, et al. Effect of A_{2A}AR activation in murine models of respiratory disorders. *Am J Physiol Lung Cell Mol Physiol*. 2006;290:L1036–L1043.
68. Nadeem A, Fan M, Ansari HR, et al. Enhanced airway reactivity and inflammation in A_{2A} adenosine receptor-deficient allergic mice. *Am J Physiol Lung Cell Mol Physiol*. 2007;292(6):L1335–L1344.
69. Haskó G, Xu DZ, Lu Q, et al. Adenosine A2A receptor activation reduces lung injury in trauma/hemorrhagic shock. *Crit Care Med*. 2006;34(4):1119–1125.
70. Thiel M, Chouker A, Ohta A, et al. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. *PLoS Biol*. 2005;3:e174.
71. Bevan N, Butchers PR, Cousins R, et al. Pharmacological characterisation and inhibitory effects of (2R,3R,4S,5R)-2-(6-amino-2-[(1S)-2-hydroxy-1-(phenylmethyl)ethyl]amino}-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydro-3,4-furandiol, a novel ligand that demonstrates both adenosine A(2A) receptor agonist and adenosine A(3) receptor antagonist activity. *Eur J Pharmacol*. 2007;564(1–3):219–225.
72. Luijk B, van den Berge M, Kerstjens HA, et al. Effect of an inhaled adenosine A2A agonist on the allergen-induced late asthmatic response. *Allergy*. 2008;63(1):75–80.
73. Rimmer J, Peake HL, Santos CM, et al. Targeting adenosine receptors in the treatment of allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy*. 2007;37(1):8–14.
74. Mantell SJ, Stephenson PT, Monaghan SM, et al. Inhaled adenosine A(2A) receptor agonists for the treatment of chronic obstructive pulmonary disease. *Bioorg Med Chem Lett*. 2008;15;18(4):1284–1287.
75. Okonkwo DO, Reece TB, Laurent JJ, et al. A comparison of adenosine A2A agonism and methylprednisolone in attenuating neuronal damage and improving functional outcome after experimental traumatic spinal cord injury in rabbits. *J Neurosurg Spine*. 2006;4(1):64–70.
76. Reece TB, Tribble CG, Okonkwo DO, et al. Early adenosine receptor activation ameliorates spinal cord reperfusion injury. *J Cardiovasc Med (Hagerstown)*. 2008;9(4):363–367.

77. Sullivan GW, Fang G, Linden J, et al. A2a adenosine receptor activation improves survival in mouse models of endotoxemia and sepsis. *J Infect Dis*. 2004;189:1897–1904.
78. Moore CC, Martin EN, Lee GH, et al. An A2a adenosine receptor agonist, ALT313, reduces inflammation and improves survival in murine sepsis models. *BMC Infect Dis*. 2008;8:141.
79. Németh ZH, Csóka B, Wilmanski J, et al. Adenosine A2A receptor inactivation increases survival in polymicrobial sepsis. *J Immunol*. 2006;176:5616–5626.
80. Sullivan GW, Linden J, Buster BL, et al. Neutrophil A2A adenosine receptor inhibits inflammation in a rat model of meningitis: synergy with the type IV phosphodiesterase inhibitor, Rolipram. *J Infect Dis*. 1999;180:1550–1560.
81. Odashima M, Otaka M, Jin M, et al. Selective adenosine A receptor agonist, ATL-146e, attenuates stress-induced gastric lesions in rats. *J Gastroenterol Hepatol*. 2005;20(2):275–280.
82. Odashima M, Otaka M, Jin M, et al. Attenuation of gastric mucosal inflammation induced by aspirin through activation of A2A adenosine receptor in rats. *World J Gastroenterol*. 2006;12(4):568–573.
83. Koizumi S, Odashima M, Otaka M, et al. Attenuation of gastric mucosal inflammation induced by indomethacin through activation of the A(2A) adenosine receptor in rats. *J Gastroenterol*. 2009;44 (5):419–425.

Journal of Receptor, Ligand and Channel Research

Publish your work in this journal

The Journal of Receptor, Ligand and Channel Research is an international, peer-reviewed, open access, online journal. The journal welcomes laboratory and clinical findings in the fields of biological receptors, ligands, channel and signal transduction research including: receptors and signalling; ligands; transporters, pores and channels; binding and activation; receptor

regulation; role of receptors in diseases and their treatment; molecular basis of membrane structure and functions; molecular models of membranes. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/journal-of-receptor-ligand-and-channel-research-journal>

Dovepress