

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

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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

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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

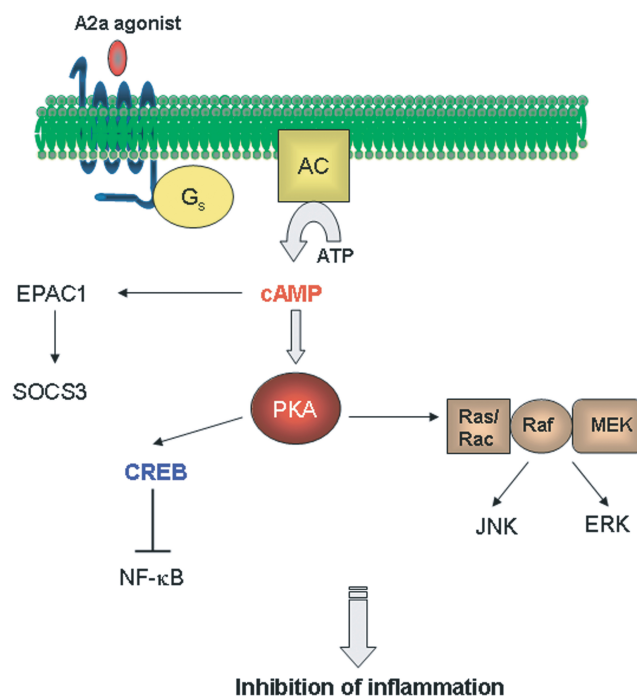


Figure 1. A2a receptor signaling pathways. A2a receptor is coupled to a G_s protein. Its activation leads to the accumulation of intracellular levels of cAMP generated by the enzyme adenylyl cyclase (AC). This latter triggers the activation of protein kinase cAMP-dependent (PKA) and subsequently activation 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.

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