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Differential Effect of Adenosine on Tumor and Normal Cell Growth: Focus on the A3 Adenosine Receptor

GIL OHANA, SARA BAR-YEHUDA, FAINA BARER, AND PNINA FISHMAN*

Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Tel-Aviv University, Rabin Medical Center, Petach-Tikva, Israel

Adenosine is an ubiquitous nucleoside present in all body cells. It is released from metabolically active or stressed cells and subsequently acts as a regulatory molecule through binding to specific A1, A_{2A}, A_{2B} and A3 cell surface receptors. The synthesis of agonists and antagonists to the adenosine receptors and their cloning enabled the exploration of their physiological functions. As nearly all cells express specific adenosine receptors, adenosine serves as a physiological regulator and acts as a cardioprotector, neuroprotector, chemoprotector, and as an immunomodulator. At the cellular level, activation of the receptors by adenosine initiates signal transduction mechanisms through G-protein associated receptors. Adenosine's unique characteristic is to differentially modulate normal and transformed cell growth, depending upon its extracellular concentration, the expression of adenosine cell surface receptors, and the physiological state of the target cell. Stimulation of cell proliferation following incubation with adenosine has been demonstrated in a variety of normal cells in the range of low micromolar concentrations, including mesangial and thymocyte cells, Swiss mouse 3T3 fibroblasts, and bone marrow cells. Induction of apoptosis in tumor or normal cells was shown at higher adenosine concentrations (>100 μM) such as in leukemia HL-60, lymphoma U-937, A431 epidermoid cells, and GH3 tumor pituitary cell lines. It was further noted that the A3 adenosine receptor (A3AR) plays a key role in the inhibitory and stimulatory growth activities of adenosine. Modulation of the A3AR was found to affect cell growth either positively or negatively depending on the concentration of the agonist, similar to the effect described for adenosine. At nanomolar concentrations, the A3AR agonists possess dual activity, i.e., antiproliferative activity toward tumor cells and stimulatory effect on bone marrow cells. In vivo, these agonists exerted anti-cancer effects, and when given in combination with chemotherapy, they enhanced the chemotherapeutic index and acted as chemoprotective agents. Taken together, activation of the A3AR, by minute concentrations of its natural ligand or synthetic agonists, may serve as a new approach for cancer therapy. J. Cell. Physiol. 186:19–23, 2001.

Adenosine, an ubiquitous purine nucleoside, is a physiological regulator of various cellular activities such as cell growth, differentiation, and cell death (Abbracchio, 1996). It is released into the extracellular environment from metabolically active or stressed cells and in order to re-enter the cells, it binds to selective G-protein-associated A1, A_{2A}, A_{2B}, and A3 membranal receptors (Stiles, 1990; Linden, 1991). Specific surface receptors for adenosine are found in nearly all cells, and almost every organ system in the body is regulated by its local release. In the heart, adenosine is known to induce a cardioprotective effect by regulating electrophysiological properties and to protect cardiac tissue through an ischemic preconditioning process. In the central nervous system, it acts as a neuroprotective agent via the suppression of neurotransmitter release and modulation of dopaminergic motor activity. Furthermore, it affects the immune system by exerting anti-inflammatory activity through the inhibition of cytokine release and platelets aggregation, induction of erythropoietin production and modulation of lymphocyte function (Gilbertsen, 1987; Soderback et al., 1991; Phillis and O'Regan, 1993;

*Correspondence to: Pnina Fishman, Laboratory of Tumor and Clinical Immunology, The Felsenstein Medical Research Institute, Rabin Medical Center, Petach-Tikva, 49100, Israel.
E-mail: pnina@mor-research.com

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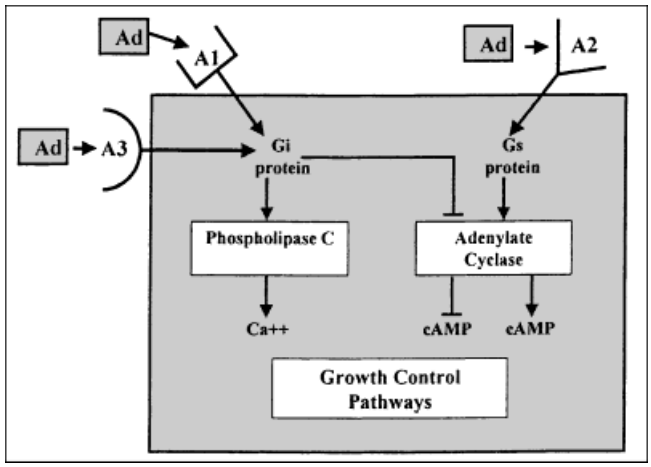

Fig. 1. The interaction of adenosine with its receptors initiates signal transduction pathways, including the adenylate cyclase and phospholipase C as effector systems.

Bouma et al., 1994; Von Lubitz et al., 1995; Lasely and Mentzer, 1996; Chen et al., 2000). This review focuses on the differential effect of adenosine or its agonists on the growth of tumor and normal cells, including the molecular mechanisms and specific receptor subtypes involved, with an emphasis on the role of the A3 adenosine receptor.

ADENOSINE: METABOLISM, TRANSPORT, AND SIGNAL TRANSDUCTION MECHANISMS

Adenosine is produced in many cell types with a basal concentration in the μM range. Its biosynthesis takes place either by the hydrolysis of 5′-ATP to 5′-ADP to 5′-AMP and to adenosine, or the intracellular enzymatic conversion of *S*-adenosylhomocysteine to adenosine. It is transported in and out of the cells by facilitated diffusion through specific nucleoside transporter proteins. Within seconds, it is metabolized by the enzyme adenosine deaminase (ADA) to inosine or is phosphorylated by adenosine kinase to form 5′-AMP. Adenosine is also released by cells undergoing necrosis or apoptosis during inflammation, shock, trauma, cancer or other stressed conditions (Burnstock, 1996a, b; Poulsen and Quinn, 1998).

The adenosine receptors belong to the G-protein-coupled family; they are of 320–420 amino acid glycoproteins with seven transmembrane domains. The overall amino acid sequence homology for the adenosine receptor subtype in different species is high (85–95%), with the exception of the A3 receptor, which exhibits only 74% homology between rat and human/sheep (Freedholm et al., 1994; Von Lubitz, 1994). Activation of the receptors by adenosine initiates a signal transduction mechanism depending on the specific receptor-associated G-protein (Fig. 1). The A1 and A3 adenosine receptors coupled with Gi proteins are associated with two effector systems, namely, adenylate cyclase and phospholipase C. The binding of adenosine or its agonists to A1 and A3 adenosine receptors, either induce inhibition of adenylate cyclase leading to a decrease in intracellular cAMP levels or stimulate phospholipase C and the release of Ca^{2+} (Gilbertsen, 1987; Soderback et al., 1991). The A_{2A} and A_{2B} receptors are associated with Gs proteins, their activation leading to an increase in intracellular cAMP (Abbracchio, 1996; Poulsen and Quinn, 1998).

EFFECT OF ADENOSINE ON NORMAL CELL GROWTH (TABLE 1)

Inhibition of normal cell growth

Adenosine's effect on the proliferation of normal cells depends upon its extracellular concentration, the specific cell surface receptor subtypes present, and the cellular transduction mechanisms activated. Adenosine and its agonists can inhibit cell growth, in a variety of normal cells, through cell-cycle arrest or apoptosis. This was demonstrated in human thymocytes, rat cardiac myocytes, rat brain astroglial cells, chick embryo sympathetic neurons, and Chinese hamster ovary cells (Kizaki et al., 1988; Abbracchio et al., 1995; Szondy, 1995; Dubey et al., 1997). Apoptosis is a normal and deliberate process that takes place when cell death is part of an organized tissue reaction, such as tissue atrophy, aging and some cases of tumor regression. In normal tissue, apoptosis can be regarded as a physiological means of maintaining tissue mass, and indeed a failure to undergo apoptosis has been implicated in

TABLE 1. Adenosine's effect on normal cell growth

Cell type	Cellular interaction	Possible mechanism	Cell growth effect	Reference
Thymocytes	?	ˇcAMP	Cell proliferation	Sandberg (1981)
	A_2 receptor	AC[1], ^Ca^{2+}	Apoptosis	Szondy (1994)
	Nucleoside transporter	Cellular uptake	Apoptosis	Szondy (1995)
Astroglial cells	A3 receptor	AC, ^Ca^{2+}	Apoptosis cell proliferation inhibition	Ceruti (1996)
Rat cardiac fibroblasts	A_{2B} receptor	AC, NO release?		Raghvendra (1997)
Murine bone marrow cells	A_{2B} receptor	AC	Cytostatic effect (G_1 phase)	Xaus (1999)
CHO cells	A3 receptor	?	Cytostatic effect (G_2/M phase)	Brambilla (1999)
Swiss Mouse, 3T3	?	^cAMP	Cell proliferation	Rozengurt (1982)
Astrocytes	Receptor mediated	?	Cell proliferation	Neary (1996)
Murine bone marrow cells	A1 and A3	AC, ^G-CSF production	Cell proliferation	Fishman (1998, 2000)
Hemopoietic stem cells	Receptor mediated	AC?	Cell proliferation	Pospisil (1993, 1995, 1998)

[1]AC: Adenylate Cyclase.

tumor development. In human thymocytes, apoptosis results from the activation of A2 receptors by 2-chloroadenosine at 40 μM concentrations, leading to an early sustained increase of cytosolic Ca^{2+} concentration and a subsequent increase in intracellular level of cAMP (Szondy, 1994). In contrast, thymocyte cell death was found to be mediated through a receptor-independent mechanism. It was shown that uptake of 2-chlorodeoxyadenosine (2-CDA) by thymocytes induced cell death. This was abolished by the nucleoside transporter inhibitor dipyridamole, suggesting the involvement of nucleotide transporters (Szondy, 1995).

In rat astroglial cells, the role of A3 adenosine receptors in the induction of apoptosis has been demonstrated. High concentrations (μM range) of the A3 adenosine agonists, IB-MECA and CL-IB-MECA, induced apoptotic cell death, while lower concentrations (nM range) were not associated with apoptosis. However, the activation of A_{2B} receptors has been reported to inhibit the proliferation of rat cardiac fibroblasts through the second messenger cAMP (Abbracchio et al., 1995; Wakade et al., 1995; Ceruti et al., 1996; Dubey et al., 1997). Interestingly, an activation of the A_{2B} receptors is known to stimulate NO release from endothelial cells and smooth muscle cells, which in turn is known to inhibit cardiac fibroblast proliferation (Vials and Burnstock, 1993; Dubey et al., 1997). This suggested a different mechanism for adenosine's inhibitory effect on rat cardiac fibroblasts. In addition, the activation of A_{2B} receptors in macrophages, derived from murine bone marrow, resulted in cell proliferation inhibition, due to a cell-cycle arrest at the G1 phase, even in the presence of M-CSF. This effect was shown to take place via the activation of adenylate cyclase and an increase in cAMP level with a subsequent upregulation of p21 and p27 (Xaus et al., 1999). A cytostatic effect of adenosine through the activation of A3 receptors has also been suggested. CHO cells transfected with human A3 receptor cDNA and incubated in the presence of μM concentrations of IB-MECA and CL-IB-MECA, induced a cytostatic effect on cell growth by arresting the cells at the G2/M phase of the cell cycle (Brambilla et al., 2000).

Stimulation of normal cell growth

The stimulation of normal cell proliferation by adenosine has been demonstrated in Swiss mouse 3T3 and 3T6 fibroblasts, thymocytes, hemopoietic cells, endothelial cells, and astrocytes (Sandberg and Fredholm, 1981; Rozengurt, 1982; Gonzales et al., 1990; Pospisil, 1993; Dusseau and Hutchims, 1998). We have recently shown that a low concentration of adenosine (4 μM) led to the proliferation of several normal cell lines, such as murine bone marrow cells, fibroblasts, muscle cells, and IM-9 lymphocytes (Fishman et al., 1998). Pharmacological studies utilizing agonists and antagonists to the various adenosine receptors, have demonstrated that bone marrow cell proliferation is mediated through the activation of the A3 receptor and to a lesser extent via the A1 adenosine receptor. The stimulatory effect was mediated by the capability of adenosine or its A1 and A3 agonists, to induce the production of granulocyte colony stimulating factor (G-CSF). These in vitro results were also confirmed in vivo (Fishman et al., 2000). Adenosine, when given to C57BL/6J mice pretreated with the chemotherapeutic agent, cyclophosphamide, demonstrated a myeloprotective effect. It restored the number of white blood cells and the percentage of neutrophils to normal values. Pospisil et al. showed that elevation of extracellular adenosine concentrations induced a radioactive effect in mice by the stimulation of hematopoiesis in the bone marrow and spleen (Sandberg and Fredholm, 1981; Pospisil et al., 1995, 1998).

INHIBITION OF TUMOR CELL GROWTH BY ADENOSINE: INCREASED CELL DEATH OR REDUCED DIVISION? (TABLE 2)

Leukemia and lymphoma

Adenosine can either induce cell death by activating specific extracellular receptors, namely, the A2 and A3

TABLE 2. Adenosine's effect on tumor cell growth

Cell type	Cellular interaction and ligand concentration	Possible mechanism	Cell growth effect	Reference
HL-60 leukemia	Nucleoside transporter (Ado[1], mM)	^ Cellular uptake	Apoptosis	Tanaka (1994)
HL-60 leukemia	A3 receptor agonist (IB-MECA, 20–40 μM)	Activated PLC**? $\uparrow Ca^{2+}$	Apoptosis	Kohno (1996); Yao (1997)
U-937 lymphoma	A3 receptor agonist (IB-MECA, 20–40 μM)	Activated PLC?$\uparrow Ca^{2+}$	Apoptosis	Kohno (1996); Yao (1997)
A431 epidermoid Ca	A1 activation (agonist <10 μM)	?	Cell growth inhibition	Khoo (1992)
A431 epidermoid Ca	A2 activation	?	Cell proliferation	Khoo (1992)
Human tumor cells	A1 activation	?	Cell growth inhibition	Colquhoun (1997)
Human CLL cells	—	—	Cell proliferation inhibition	Bajaj (1983)
K-562 leukemia, LNCaP	↑A3, ↑A2 receptors (adenosine, 4 μM)	AC, ↓telomeric signal	Cytostatic effect (G_O/G_1 phase)	Fishman (1998)
Nb2 lymphoma	Adenosine (5–25 μM)	AC, ↓telomeric signal	Cytostatic effect (G_O/G_1 phase)	Fishman (2000)
Nb2 lymphoma	↑A3, ↑A2 receptors (50 μM)	AC?	Apoptosis	Fishman (2000)

[1]Ado: Adenosine.
[2]PLC: Phospholipase C.

subtypes, or enter cells directly. In the human leukemia cell line HL-60, adenosine at mM concentrations caused an apoptosis which was not mediated via the adenosine receptors but through an active transport of adenosine into the cells. This was the result of experiments demonstrating the failure of adenosine agonists to mimic, or adenosine antagonists to block, this effect. Adenosine transport seemed to be essential for the induction of apoptosis, since the inhibition of adenosine transport into the cells by dipyridamole strongly suppressed this apoptotic effect (Tanaka et al., 1994). In HL-60 promyelocytic leukemia and U-937 hitiocytic lymphoma cells, A3 adenosine agonists, IB-MECA and CL-IB-MECA, at high concentration (20–40 μM) induced apoptosis (Kohno et al., 1996; Yao et al., 1997). In these studies, an elevation in intracellular calcium concentration was observed, which was correlated with the upregulation of the Bak gene (Farrow et al., 1995). However, low concentrations of these agonists (<1 μM) did not induce apoptosis.

We recently demonstrated, in vitro, that adenosine at low concentrations, inhibited the proliferation of Nb2 lymphoma and K-562 chronic myelogenous leukemia cell lines (Fishman et al., 2000). Moreover, adenosine's inhibitory effect on Nb2-11C lymphoma cells was shown to occur at low concentrations (5–25 μM) and to be dose dependent. Adenosine induced an arrest of the cells in the G0/G1 phase of cell cycle and indeed a decrease in the telomeric signal (Fishman et al., 2000), thus suggesting a cytostatic rather than apoptotic effect, mediated through the A3 adenosine receptor. Telomeres are repeated DNA sequences that guard the ends of chromosomes, serving as a checkpoint for cell-cycle progression, thus regulating cell senescense and apoptosis. This amplification of telomeres has been related to invasive and metastatic potential of tumor cells with a well-established correlation between decreased telomeric signal, cell-cycle arrest, and cell death (Kallassy et al., 1998; Multani et al., 1999).

In another study, adenosine was shown to induce a differential effect on tumor and normal cell growth. The proliferation of lymphocytes derived from patients with chronic lymphocytic leukemia was suppressed by adenosine, whereas that of normal lymphocytes was inhibited to a lesser extent (Bajaj et al., 1983). Hence, the extracellular adenosine concentration may be a crucial factor in determining the cell progression pathway, either to apoptosis or a cytostatic state.

Solid tumors

In A431 human epidermoid carcinoma cells, low concentration of adenosine (< 10 μM) induced the inhibition of cell growth through the activation of A1 receptors, but promoted cell proliferation at higher concentrations through the A2 receptors (45). The capability of the A1 agonists to exert an inhibitory effect on human tumor cells has been reported (Colquhoun and Newsholme, 1997).

We have recently demonstrated that adenosine inhibited the growth of LNCaP human prostate adenocarcinoma and murine B16-melanoma in vitro (Fishman et al., 1998). The A3 adenosine receptor agonist, IB-MECA inhibited the proliferation of murine B16-F10 melanona and human colon adenocarcinoma cell lines (unpublished data). This unpublished data also include in vivo experiments showing a significant inhibition of metastatic lung foci with prolongation of survival time in mice inoculated intravenously with melanoma (B16-F10) cells.

CONCLUSIONS

This review suggests that adenosine, a regulatory molecule with widespread physiological effects in almost every cell and body system, acts as a potent regulator of cell growth. This effect depends on the extracellular concentration and expression of different adenosine receptor subtypes and the signal transduction mechanisms activated following the binding of specific agonists. An important role for the A3 adenosine receptor in modulating cell growth has been presented. Adenosine or its various specific receptor agonists induces a variety of cell growth effects, ranging from apoptosis through cytostatic effect to the stimulation of cell proliferation. The importance of extracellular concentration of adenosine or its A3 receptor agonist was demonstrated by showing a lethal effect on tumor or normal cell growth at high concentrations, while more restrained effects such as cell cytostatic effects on tumor cells or even normal cell proliferation at the low concentrations. Moreover, several evidences are presented suggesting the possible involvement of agonists to the A3 adenosine receptor in the regulation of cell-cycle progression. Synthetic A3AR agonists at low concentrations represent selective agents with a dual effect on tumor and normal cell growth. These molecules inhibit tumor cell growth, while simultaneously stimulating normal cell proliferation such as bone marrow cells. This could be exploited to develop unique compounds with the ability to suppress tumor cell growth, alone or in combination with chemotherapy, while preventing the myelotoxic effects of chemotherapy.

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