Adenosine Inhibits Collagen and Protein Synthesis in Cardiac Fibroblasts

Role of A2B Receptors

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Abstract—The objective of this study was to characterize the effects of exogenous and endogenous (cardiac fibroblast-derived) adenosine on [3H]proline and [3H]leucine incorporation, which are reliable markers of collagen and total protein synthesis, respectively, in rat left ventricular cardiac fibroblasts. Growth-arrested confluent cardiac fibroblast monolayers were stimulated with 2.5% fetal calf serum (FCS) in the presence and absence of adenosine, 2-chloroadenosine (stable adenosine analogue), or modulators of adenosine levels including (1) erythro-9-(2-hydroxy-3-nonyl) adenine (adenosine deaminase inhibitor), (2) dipyridamole (adenosine transport blocker), and (3) iodotubericidin (adenosine kinase inhibitor). All agents inhibited in a concentration-dependent fashion FCS-induced [3H]proline and [3H]leucine incorporation. These effects were blocked by KF17837 (selective A2 antagonist) and 1,3-dipropyl-8-(p-sulfophenyl)xanthine (A1/A2 receptor antagonist) but not by 8-cyclopentyl-1,3-dipropylxanthine (selective A1 antagonist), thus excluding the participation of A1 receptors. The lack of effect of CGS21680 (selective A2A agonist) excluded involvement of A2A receptors, thus suggesting a major role for A2B receptors. Comparisons of the inhibitory potencies of N6-cyclopentyladenosine (selective A1 agonist), 5′-N-ethylcarboxamidoadenosine (A1/A2 agonist), and 5′-N-methylcarboxamidoadenosine (A1/A2 agonist) were consistent with that of an A2B receptor subtype mediating the inhibitory effects. We conclude that adenosine inhibits FCS-induced collagen and total protein synthesis in cardiac fibroblasts via activation of A2B receptors. These studies suggest, but do not prove, that endogenous adenosine may protect against cardiac fibrosis. (Hypertension. 1998;31:943-948.)

Key Words: adenosine • fibroblasts • myocardial infarction • extracellular matrix • collagen • hypertrophy

Diastolic and/or systolic dysfunction in heart failure is caused in part by pathological distortions of the ventricular architecture. Multiple cellular mechanisms contribute to this phenomenon, including cardiac fibrosis, proliferation/hypertrophy of CFs, and rearrangement/hypertrophy of cardiac myocytes.1–4 Cardiac fibrosis occurs when steady state levels of ECM proteins are increased. In this regard, the accumulation of fibrillar collagen in the extracellular space not only contributes to cardiac enlargement but also disrupts the electrical and mechanical properties of the myocardium.1,2 Moreover, increased deposition of ECM proteins, particularly collagen, triggers and supports the proliferation/hypertrophy of CFs and rearrangement/hypertrophy of cardiac myocytes.1–4 Because cardiac fibrosis appears to play a pivotal role in all mechanisms leading to distortions of ventricular architecture, it is important to elucidate the biochemical/cellular mechanisms leading to this disease.

Although the proximate cause of cardiac fibrosis is an increased production and/or reduced degradation of ECM proteins by CFs,1–4 the root causes of cardiac fibrosis involve those factors that regulate the size, number, and synthetic activity of CFs. Unlike cardiac myocytes, endogenous factors (circulating and cardiac cell–derived) rather than hemodynamic forces induce abnormal behavior of CFs.1–4 However, the endogenous factors that regulate CFs are not well understood, and a number of circulating and cardiac cell–derived factors appear to participate.1–4 In a normal heart, the balanced generation of circulating and cardiac cell–derived inhibitors of CFs (such as atrial natriuretic peptide and nitric oxide) and promoters of CFs (such as platelet-derived growth factor, fibroblast growth factor, transforming growth factor-β, insulinlike growth factor-1, angiotensin II, and endothelin) is responsible for regulating CFs.9–12 Disruption of this balance could trigger a vicious cycle of events: increased ECM production by CFs, proliferation and hypertrophy of CFs, and further ECM synthesis by the enlarged and more numerous CFs. Therefore, endogenous factors that brake CF activity and...
are generated in substantial amounts locally within the heart wall may play a major cardioprotective role.

In this regard, adenosine may be an important factor. Adenosine is synthesized by the cardiac wall and exerts numerous cardioprotective and antivasoocclusive actions.\(^{5}\) Cardiomyocytes,\(^{10}\) vascular smooth muscle cells,\(^{11,12}\) and endothelial cells, both vascular and cardiac,\(^{5,10}\) have several metabolic pathways for generating large amounts of adenosine. For example, it has been shown that endothelial cells synthesize adenosine and have an adenosine pool that is two to three times greater than that of hepatocytes.\(^{6,10}\) Moreover, we have recently shown that CFs, which constitute 60% of the heart wall,\(^{2}\) can also synthesize adenosine.\(^{6}\) Therefore, substantial amounts of adenosine are synthesized locally within the cardiac wall, in part by CFs, thus ensuring pharmacologically active levels of adenosine in the heart.

We have also recently discovered that exogenous as well as endogenous adenosine inhibits FCS-induced proliferation of CFs.\(^{5}\) Because some factors that inhibit cell proliferation also inhibit cellular hypertrophy and ECM synthesis, we hypothesize that adenosine may be an endogenous factor that attenuates hypertrophy of and collagen synthesis by CFs. Accordingly, the aims of the present study were to determine whether exogenous and endogenous (CF-derived) adenosine inhibits collagen and total protein synthesis by ventricular CFs and to determine which adenosine receptor subtype(s) is (are) involved.

**Methods**

Adenosine, Cl-Ad (stable adenosine agonist; EC\(_{50}\) on adenylyl cyclase activity mediated by \(A_1\) [rat fat cells], \(A_{2A}\) [rat pheochromocytoma cells], and \(A_{2B}\) [human fibroblasts] receptors are 100, 460, and 15,000 nmol/L, respectively\(^{13}\)), ENDA (adenosine deaminase inhibitor\(^{14}\)), DIP (adenosine transport blocker\(^{14}\)), and IDO (adenosine kinase inhibitor\(^{14}\)) were purchased from Sigma Chemical Co. CPA \((\beta\text{-sulfophenylxanthine})\), DPCPX \((8\text{-cyclopentyl-1,3-dipropylxanthine})\), and DIPSPX \((1,3\text{-dipropyl-8-p-sulfophenylxanthine})\) were purchased from Research Biochemicals International, Sprague-Dawley male rats weighing 150 to 200 g were obtained from Charles River (Wilmington, Mass), and left ventricular CFs were cultured by the method of Farivar et al\(^{15}\) using cardiomyocyte digestion with collagenase and selective plating as described by us previously.\(^{8}\) CFs in second and third passages were used to study the effects of exogenous and endogenous adenosine on FCS-induced collagen and protein synthesis. CF purity (>98%) was confirmed by feeding of DME/F12 medium containing 10% FCS under standard tissue culture conditions. CFs were made quiescent by feeding of DME/F12 containing 0.4% BSA (Sigma) for 48 hours. Collagen and protein synthesis were initiated by treating growth-arrested CFs for 36 and 24 hours, respectively, with DME/F12 supplemented with 2.5% FCS and without or with adenosine receptor agonists, adenosine receptor antagonists, and/or modulators of adenosine levels. For collagen synthesis, the cells were treated for 36 hours in the presence of \(L-[\text{3}^\text{H}]\text{proline}\) (1 \(\mu\text{Ci/mL}\)), whereas for total protein synthesis after 20 hours of treatment, the cells were pulsed for 4 hours with \(L-[\text{3}^\text{H}]\text{leucine}\) (1 \(\mu\text{Ci/mL}\)). The experiments were terminated by washing the cells twice with Dulbecco’s PBS and twice with ice-cold trichloroacetic acid (10%). The precipitate was solubilized in 500 \(\mu\text{L}\) of 0.3 N NaOH and 0.1% SDS after incubation at 50°C for 2 hours. Aliquots from four wells for each treatment with 10 mL scintillation fluid were counted in a liquid scintillation counter.

We have previously demonstrated that adenosine inhibits CF proliferation. Hence, to confirm that the decrease in collagen and protein synthesis was not due to a decrease in cell number, the experiments were conducted in confluent monolayers in which changes in cell number were precluded. Also, cell counting was performed in cells treated in parallel to the cells used for the collagen and total protein synthesis studies, and the data were normalized to cell number.

All experiments were performed in quadruplicate with three to six separate cultures, and the data are presented as mean±SEM. Statistical analysis was performed using ANOVA, paired Student’s \(t\) test, and Fisher’s least significant difference test as appropriate. A value of \(P<0.05\) was considered statistically significant.

**Results**

Compared with growth-arrested CFs treated with 0.25% FCS for 48 hours, treatment with 2.5% FCS stimulated proline and
leucine incorporation by 6- to 8-fold (*P < .001; data not shown). Adenosine and Cl-Ad significantly and dose-dependently inhibited FCS-induced proline and leucine incorporation, with the lowest EC₅₀ being 10 nmol/L (Fig 1). Adenosine and Cl-Ad inhibited proline incorporation by 50% at ≈80 and 10 µmol/L, respectively, and inhibited leucine incorporation by 50% at ≈100 and 8 µmol/L, respectively. As shown in Fig 2, the inhibitory effects of adenosine were significantly enhanced by EHNA. EHNA, IDO, and DIP inhibited proline and leucine incorporation in a concentration-dependent manner (Fig 3). EHNA, IDO, and DIP inhibited proline incorporation by 50% at approximately 75, 10, and 10 µmol/L, respectively, and inhibited leucine incorporation by 50% at ≈50, 10, and 10 µmol/L, respectively. Compared with EHNA, DIP and IDO were more effective inhibitors of proline and leucine incorporation. All possible two-way combinations of DIP (1 µmol/L), IDO (0.5 µmol/L), and EHNA (10 µmol/L) decreased FCS-induced proline and leucine incorporation in an additive manner, and FCS-induced proline and leucine incorporation were reduced to almost basal levels by the three-way combination (Fig 4). Fig 5 illustrates the relative potency of a number of adenosine receptor agonists on FCS-induced proline and leucine incorporation. For both proline and leucine incorporation, the potency order was Cl-Ad = MECA > NECA > CPA > CGS21680. KF17837 and DPSPX, but not DPCPX, significantly reversed the inhibitory effects of Cl-Ad, EHNA, and DIP on FCS-induced proline and leucine incorporation (Fig 6). No treatments caused cell

Figure 1. Inhibition of proline and leucine incorporation in CFs by adenosine and Cl-Ad. All wells were stimulated with 2.5% FCS. Proline or leucine incorporation in control wells (FCS only) was 3.1 ± 0.05 × 10⁴ dpm/1.5 × 10⁵ CFs and 2.5 ± 0.06 × 10⁴ dpm/1.5 × 10⁵ CFs, respectively (with cell counts of 1.52 ± 0.048 × 10⁵ cells per well). Cell counts in CFs treated with 10⁻¹⁰ to 10⁻⁶ mol/L of either adenosine or Cl-Ad were not different from those in controls (<3% variation). Values are mean ± SEM from 4 to 6 separate experiments, each conducted in quadruplicate. *P < .05 from control; †P < .05 from EHNA.

Figure 2. Inhibition of proline and leucine incorporation in CFs by exogenous adenosine in the absence and presence of EHNA. All wells were stimulated with 2.5% FCS. Control proline or leucine incorporation was 3.2 ± 0.08 × 10⁴ dpm/1.5 × 10⁵ CFs and 2.87 ± 0.07 × 10⁴ dpm/1.5 × 10⁵ CFs, respectively, in the absence of EHNA (with cell counts of 1.47 ± 0.06 × 10⁵ cells per well), and 2.9 ± 0.024 × 10⁴ dpm/1.5 × 10⁵ CFs and 2.41 ± 0.068 × 10⁴ dpm/1.5 × 10⁵ CFs, respectively, in the presence of EHNA. Cell counts in CFs treated with EHNA, adenosine, or EHNA + adenosine were not different from those in CFs without any treatment (<3% variation). Values are mean ± SEM from 4 to 6 separate experiments, each conducted in quadruplicate. *P < .05 from respective control; †P < .05 from no EHNA.

Figure 3. Inhibition of proline and leucine incorporation in CFs by EHNA, IDO, and DIP. All wells were stimulated with 2.5% FCS. Control proline or leucine incorporation was 2.97 ± 0.01 × 10⁴ dpm/1.5 × 10⁵ CFs and 2.67 ± 0.01 × 10⁴ dpm/1.5 × 10⁵ CFs, respectively (with cell counts of 1.6 ± 0.08 × 10⁵ cells per well). Cell counts in CFs treated with EHNA, IDO, or DIP were not different from those in controls (<3% variation). Values are mean ± SEM from 4 to 6 separate experiments, each conducted in quadruplicate. *P < .05 from control.

Figure 4. Inhibition of proline and leucine incorporation in CFs by EHNA (10 µmol/L), IDO (0.5 µmol/L), and/or DIP (1 µmol/L). All wells were stimulated with 2.5% FCS. Control proline or leucine incorporation was 2.85 ± 0.07 × 10⁴ dpm/1.5 × 10⁵ CFs and 2.46 ± 0.057 × 10⁴ dpm/1.5 × 10⁵ CFs, respectively (with cell counts of 1.55 ± 0.06 × 10⁵ cells per well). Cell counts in CFs treated with EHNA, IDO, and/or DIP were not different from those in controls (<3% variation). Values are mean ± SEM from 3 separate experiments, each conducted in quadruplicate. *P < .01 from control; †P < .05 from EHNA.
death (trypan blue exclusion) or cell detachment (cell counts in supernatant and on well surface), except for 100 μmol/L of EHNA, DIP, and IDO, which decreased cell viability by approximately 6%.

**Discussion**

Our results demonstrate that treatment of CFs with adenosine, with stable adenosine analogues (Cl-Ad, MECA, and NECA), and with agents that elevate endogenous adenosine (EHNA, IDO, and DIP) inhibits FCS-induced proline and leucine incorporation. In this study we examined the incorporation of proline and leucine as indices of collagen and total protein synthesis, respectively. Although the interpretation of proline incorporation is straightforward, the interpretation of total protein synthesis must be made cautiously. Because our studies were conducted in CFs that were neither increasing nor decreasing in cell number, changes in total protein synthesis can be interpreted to mean either changes in cell mass or changes in ECM production or both. Because proline incorporation was altered by the treatments, the changes in total protein synthesis were no doubt in part due to alterations in collagen production. However, since total protein synthesis was altered by the various treatments more than collagen synthesis, changes in cell mass must also have contributed to the observed changes in leucine incorporation. Therefore, our data indicate that exogenous and endogenous adenosine inhibits both collagen production and cellular hypertrophy induced by FCS.

Because the inhibitory effects of adenosine are mimicked by MECA and NECA (agonists with affinity for A1, A2A, and A2B receptors) but not by CPA and CGS21680 (agonists selective for A1 and A2A receptors, respectively), the inhibitory effects of adenosine on proline and leucine incorporation are most likely mediated via A2B receptors rather than A1 or A2A receptors. This inference is corroborated by the observation that MECA is more potent than NECA as an inhibitor of proline and leucine incorporation. Because NECA has a higher affinity for A1 and A2A receptors compared with MECA,13 if A1 or A2A receptors mediate the inhibitory effects of adenosine, then NECA would be more potent than MECA, which is not the case. Moreover, the inhibition mediated by adenosine receptors is attenuated by KF17837 (a selective A2 receptor agonist) and by DPSPX (an A1/A2 receptor antagonist) but not by DPCPX (a selective A1 receptor antagonist). Taken together, our findings provide the first evidence that exogenous as well as CF-derived adenosine inhibits serum-induced collagen and total protein synthesis via the A2B receptor.

Our contention that the inhibitory effects of adenosine are mediated via A2B receptors is further supported by the recently proposed and endorsed subclassification of A2A and A2B receptors.19 Gurden et al20 have recently demonstrated that the relative potencies of CGS21680 and NECA can be used as a reference to differentiate A2A from A2B receptors. When the effects of CGS21680 are as potent as those of NECA, this implicates the A2A receptor. However, when CGS21680 is much less potent than NECA, this indicates that the observed effects are mediated via activation of the A2B receptor subtype. In the present study, compared with CGS21680, NECA was more effective in mimicking the inhibitory effects of adenosine, which further substantiates our conclusion that the inhibitory effects of adenosine are mediated via A2B receptors.

The EC50s of Cl-Ad and NECA for A2B receptor–mediated stimulation of adenyl cyclase in human fibroblast membranes are 15 and 1.9 μmol/L, respectively.13 In our para-
digram, Cl-Ad inhibits collagen and protein synthesis by 50% at \( \approx 10 \) \( \mu \)mol/L, so the potency of Cl-Ad is consistent with an A\(_{2B} \) receptor–mediated process. It should be pointed out, however, that the concentration of Cl-Ad that inhibits collagen and protein synthesis by 50% is not the same as an IC\(_{50} \), ie, the concentration that causes a half-maximal effect. In our cultured rat CFs, NECA is less potent than Cl-Ad with regard to inhibition of collagen and protein synthesis. This discrepancy cannot be attributed to endogenous adenosine competing for A\(_{2B} \) receptors, since such competition would not alter the relative potencies of Cl-Ad versus NECA, ie, both agonists would be similarly affected. Moreover, because the studies were performed under exactly the same conditions, the results cannot be attributed to different amounts of FCS or differences in the CFs. A possible explanation for the reverse order of potency, ie, Cl-Ad > NECA rather than NECA > Cl-Ad, is that rat A\(_{2B} \) receptors and human A\(_{2B} \) receptors differ pharmacologically. In this regard, species differences in the rank order potency of adenosine receptor agonist and antagonist for adenosine receptor subtypes are common.\(^{21,22} \) However, in a recent study we observed that the inhibitory effect of Cl-Ad on FCS-induced growth of human aortic smooth muscle cells was greater than that of NECA.\(^{23} \)

A\(_{2B} \) receptors are positively coupled with adenylyl cyclase, and their activation results in a significant increase in cAMP levels.\(^{19} \) Stimulation of CFs with adenosine has been shown to elevate cAMP levels, and cAMP in turn has antiproliferative effects on CFs.\(^{24} \) Therefore, the inhibitory effect of adenosine on collagen and protein synthesis by CFs is most likely mediated largely via the second messenger cAMP; however, the participation of other mechanism(s) cannot be ruled out. Activation of A\(_{2B} \) receptors by adenosine stimulates NO release from endothelial cells,\(^{25,26} \) and we have recently observed that adenosine amplifies lipopolysaccharide-induced NO release from vascular smooth muscle cells.\(^{27} \) Because NO inhibits CF proliferation,\(^{28} \) this provides an additional pathway through which adenosine could inhibit collagen and protein synthesis by CFs.

The physiological effects of adenosine are governed in part by the rapid rate of elimination of adenosine from the extracellular space. Elimination of adenosine from the interstitial space is mediated by facilitated transport of adenosine into cells and also by metabolism of adenosine to inosine by adenosine deaminase,\(^{14} \) and to AMP by adenosine kinase.\(^{6} \) Inhibition of the enzyme adenosine deaminase by EHNA and the enzyme adenosine kinase by IDO, as well as the inhibition of adenosine transport and metabolism by DIP, increases endogenous levels of adenosine.\(^{14} \) Hence, these three compounds were used in the present study to increase endogenous levels of adenosine so as to evaluate the effects of endogenously generated adenosine on FCS-induced prolne and leucine incorporation.

EHNA and DIP inhibited FCS-induced prolne and leucine incorporation, and KF17837 and DPSPX significantly reversed the inhibitory effects of EHNA and DIP. Also, the inhibitory effects of EHNA, IDO, and DIP were significantly enhanced when CFs were treated with a combination of these agents. These findings support our contention that the inhibitory effects of these agents on collagen and protein synthesis in CFs are mediated via generation of adenosine. Moreover, the finding that DPSPX, a selective A\(_{1} \) receptor antagonist, did not reverse the inhibitory effects of EHNA and DIP on CFs strongly suggests that the inhibitory effects of endogenous adenosine are mediated via A\(_{2B} \) receptors.

KF17837 and DPSPX only partially prevented the inhibitory effects of Cl-Ad, EHNA, and DIP, suggesting that the concentrations of KF17837 and DPSPX used were not maximal. Although the concentrations of DPSPX (10\(^{-8} \) mol/L) and KF17387 (10\(^{-7} \) mol/L) were high enough to partially block A\(_{2B} \) receptors, we were unable to use higher concentrations of these antagonists because at higher concentrations they have nonspecific effects. For instance, concentrations of KF17837 and DPSPX higher than 10\(^{-9} \) mol/L and 10\(^{-8} \) mol/L, respectively, inhibit FCS-induced growth of CFs by almost 40% to 50% (data not shown). Because we were investigating whether adenosine inhibits collagen and protein synthesis in CFs via A\(_{2B} \) receptors, it was necessary to use a concentration of KF17837 and DPSPX that did not per se markedly decrease collagen and protein synthesis.

Could our in vitro finding that adenosine inhibits serum-induced collagen and total protein synthesis be of physiological relevance under in vivo situations? Because FCS contains a battery of growth factors (eg, platelet-derived growth factor, epidermal growth factor, fibroblast growth factor, angiotensin II, endothelin, and norepinephrine) that stimulate cardiac hypertrophy/remodeling, the inhibitory effects of adenosine on FCS-induced activation of CFs suggest a physiological role for adenosine as a regulator of protein synthesis by CFs. The fact that low concentrations of adenosine inhibited collagen and total protein synthesis in CFs in the presence, but not absence, of EHNA suggests that although adenosine effectively inhibits collagen and protein synthesis in CFs, its effects are underestimated in the present series of experiments, since they were conducted in the presence of FCS, which contains adenosine deaminase. Because under normal conditions in vivo most of the adenosine deaminase is localized within cells, the adenosine in the extracellular compartment will be available in active form to mediate the physiological inhibitory effects on CF activity. Moreover, since adenosine is synthesized via multiple pathways by cardiac fibroblasts,\(^{9} \) myocytes,\(^{10,24} \) and endothelial cells,\(^{6,10} \) this ensures pharmacologically active steady state levels of adenosine locally at the interface between endothelial and CFs, as well as myocytes and cardiac fibroblasts. In contrast, under pathological conditions associated with decreased adenosine synthesis or increased adenosine deaminase leakage from cells, extracellular levels of adenosine would be diminished, and this would result in decreased inhibitory effects of adenosine. In this regard, recent data from our laboratory provide evidence that adenosine deaminase may participate in at least two disease states associated with increased risk of cardiovascular disease, ie, sickle cell anemia and aging/hypertension.\(^{9} \) However, future studies are needed to confirm or deny this role of adenosine deaminase.

In conclusion, we provide evidence that both exogenous and CF-derived adenosine inhibit FCS-induced collagen and total protein synthesis by CFs. Our findings suggest, but do not prove, that adenosine produced by CFs may play a role as
a local inhibitory agent and that decreased synthesis of adenosine by CFs or increased catabolism of adenosine by adenosine deaminase or adenosine kinase may contribute to the abnormal synthesis and deposition of collagen and hypertrophy of CFs observed in cardiac fibrosis associated with hypertension, myocardial infarction, and reperfusion injury after ischemia.

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References
4. Zhu X, Assoian RK. Integrin-dependent activation of MAP kinase: a link to a local inhibitory agent and that decreased synthesis of adenosine by CFs or increased catabolism of adenosine by adenosine deaminase or adenosine kinase may contribute to the abnormal synthesis and deposition of collagen and hypertrophy of CFs observed in cardiac fibrosis associated with hypertension, myocardial infarction, and reperfusion injury after ischemia.

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References
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References
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