Inhibiting adenosine deaminase modulates the systemic inflammatory response syndrome in endotoxemia and sepsis

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Adanin, Simon, Igor V. Yalovetskiy, Beth A. Nardulli, Albert D. Sam II, Zivojn S. Jonjev, and William R. Law. Inhibiting adenosine deaminase modulates the systemic inflammatory response syndrome in endotoxemia and sepsis. Am J Physiol Regulatory Integrative Comp Physiol 282: R1324–R1332, 2002; 10.1152/ajpregu.00373.2001.—By pharmacological manipulation of endogenous adenosine, using chemically distinct methods, we tested the hypothesis that endogenous adenosine tempers proinflammatory cytokine responses and oxyradical-mediated tissue damage during endotoxemia and sepsis. Rats were pretreated with varying doses of pentostatin (PNT; adenosine deaminase inhibitor) or 8-sulfophenyltheophylline (8-SPT; adenosine receptor antagonist) and then received either E. coli endotoxin (lipopolysaccharide; 0.01 or 2.0 mg/kg) or a slurry of cecal matter in 5% dextrose in water (200 mg/kg). Resultant levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10 were measured in serum and in liver and spleen. Untreated, 2 mg/kg lipopolysaccharide elevated serum TNF-α, IL-1β, and IL-10. PNT dose dependently attenuated, without abating, the elevation in serum TNF-α and IL-1β and raised liver and spleen IL-10. PNT also attenuated elevation of TNF-α in serum, liver, and spleen at 4 and 24 h after sepsis induction, and 8-SPT resulted in higher proinflammatory cytokines. Modulating endogenous adenosine was also effective in exacerbated (8-SPT) or diminished (PNT) tissue peroxidation. Survival from sepsis was also improved when PNT was used as a posttreatment. These data indicate that endogenous adenosine is an important modulatory component of systemic inflammatory response syndromes. These data also indicate that inhibition of adenosine deaminase may be a novel and viable therapeutic approach to managing the systemic inflammatory response syndrome without ablating important physiological functions.

shock; cytokines; oxyradical

Our laboratory has demonstrated that endogenous adenosine is involved in maintaining elevated resting hepatosplanchnic (23, 24) and skeletal muscle perfusion in sepsis (24), in part via stimulation of nitric oxide synthase (34, 36). It is not clear whether adenosine’s role as an endogenous modulator of responses to inflammatory processes can be exploited to better manage systemic inflammatory response syndromes (SIRS).

Most of the work describing the immunomodulating abilities of adenosine have been performed in vitro. Adenosine has been reported to inhibit β-galactosidase secretion (30) and chemiluminescence (15) from zymosan particle-stimulated mouse peritoneal macrophages. Adenosine has also been shown to inhibit tumor necrosis factor (TNF)-α produced by monocytes in response to endotoxin [lipopolysaccharide (LPS)] (11) and reduce leukocyte accumulation and TNF-α production after carrageenan stimulation (8). However, these in vitro findings cannot be easily extrapolated to the complex in vivo immune response associated with sepsis. Firestein et al. (12) explored this question by using GP-1–515, an adenosine kinase inhibitor, a proprietary compound that purportedly inhibited adenosine kinase. This compound was able to inhibit LPS-mediated increases in TNF-α and improve survival, effects that were blocked with adenosine receptor antagonism. However, effects were only seen in the presence of GP-1–515, which was structurally similar to adenosine. Thus it is not clear whether endogenous adenosine is a significant signaling molecule for SIRS.

The following experiments were designed to test the hypothesis that endogenous adenosine, produced as a consequence of a septic challenge in vivo, serves to directly temper proximal cytokine responses and tissue products of lipid peroxidation, as measured by thiobarbituric acid-reactive substances (TBARS). Specifically, two chemically distinct approaches were used to test the hypothesis. First, the adenosine receptor antagonist 8-sulfophenyltheophylline (8-SPT) was used to determine whether blockade of adenosine receptors would exacerbate early proinflammatory cytokine and TBARS concentrations after a septic challenge. Second, the adenosine deaminase inhibitor 2-deoxycoformycin was used to determine whether reducing the degradation of endogenous adenosine would amplify the tempering influences of adenosine on early proinflammatory cytokine and TBARS concentrations after a septic challenge. Haskó et al. (13) reported that...
Materials

**METHODS**

Adenosine-stimulated release of the anti-inflammatory cytokine interleukin (IL)-10 is partially responsible for the ability of adenosine to regulate TNF-α release in vitro. Thus we also tested the hypothesis that endogenous adenosine has effects on IL-10 after a septic challenge in vivo similar to those reported in vitro.

**Materials**

8-SPT. 8-SPT (Research Biochemicals International, Nat-tuck, MA), a nonselective (A1/A2/A3) but highly specific (no phosphodiesterase inhibition) adenosine receptor antagonist (3, 9, 14), was solubilized in sterile water to obtain an injectate volume of 1 ml/kg at a dose of 20 mg/kg every 8 h. The dose was determined based on pilot studies, which obtained and maintained complete blockade of hemodynamic effects of an exogenously administered adenosine (1 mmol/kg) bolus.

2-Deoxycoformycin. 2-Deoxycoformycin (pentostatin, Supergen, Dublin, CA), a potent inhibitor of adenosine deaminase, was solubilized in sterile water to concentrations ranging from 10⁻⁶ to 1.0 mg/ml at final injection volumes of 1 ml/kg.

**Animals**

The experiments reported herein were approved by the Animal Care and Use Committee of the University of Illinois and were conducted according to the principles set forth in the Guide for the Care and Use of Laboratory Animals, revised in 1996. Male Sprague-Dawley rats (Harlan, IN), weighing 300–350 g, were housed at constant temperature with 10- and 14-h periods of light and dark exposure, respectively. Animals were allowed access to standard rat chow and water ad libitum during an acclimation period of at least 7 days before use in these experiments.

**Protocol 1: Pentostatin Dose Response After LPS**

To determine the optimal attenuating dose of pentostatin, we used a fixed septic challenge with *Escherichia coli* LPS (2 mg/kg; serotype 0127:B8, lot 10692.2JA; Difco Labs, Detroit, MI). After weighing, rats received an intraperitoneal (IP) injection of one of five doses of pentostatin or sterile water (treatment control). One hour later, rats were challenged with 2 mg/kg LPS or saline IP (challenge control). Two hours after LPS injection, rats were lightly anesthetized with isoflurane. The chest and abdomen were immediately opened, and blood was withdrawn via cardiac puncture. Blood was allowed to clot, and, after centrifugation, serum was assayed directly after dilution. Tissue samples were pulverized under liquid nitrogen with homogenizing buffer [10 mM Trizma·HCl, 1 mM EGTA, 350 mM sucrose, 5 mM sodium azide (NaN₃), 10 mM β-mercaptoethanol, 0.02 mM phenylmethylsulfonyl fluoride, 50 mM sodium fluoride (NaF), 1 mg/ml pepstatin, 1 mg/ml leupeptin, pH 7.5, at 4°C]. A total of 10× volume of homogenization buffer was added to the tissue sample and homogenized with an Omni Polytron homogenizer with small size tip for 30 s bursts while on ice. The homogenate was centrifuged at 100,000 g for 60 min at 4°C, and the supernatant was assayed immediately after dilution.

**Cytokine Assays**

Cytokines were measured from serum or tissue by using commercially available ELISA assays with the use of rat antibodies to each specific cytokine (R&D Systems, Minneapolis, MN). Serum was assayed directly after dilution. Tissue samples were pulverized under liquid nitrogen with homogenizing buffer [10 mM Trizma·HCl, 1 mM EGTA, 350 mM sucrose, 5 mM sodium azide (NaN₃), 10 mM β-mercaptoethanol, 0.02 mM phenylmethylsulfonyl fluoride, 50 mM sodium fluoride (NaF), 1 mg/ml pepstatin, 1 mg/ml leupeptin, pH 7.5, at 4°C]. A total of 10× volume of homogenization buffer was added to the tissue sample and homogenized with an Omni Polytron homogenizer with small size tip for 3 × 10 s bursts while on ice. The homogenate was centrifuged at 100,000 g for 60 min at 4°C, and the supernatant was assayed immediately after dilution.

**TBARS Assay**

TBARS were determined according to the methods of Ohkawa et al. (26) by using malondialdehyde to generate a standard curve. Samples of liver and spleen were homoge-nized on ice in 1.10 wt/vol of 1.15% KCl buffer containing 0.01% butylated hydroxytoluene. Samples were centrifuged at 21,000 g for 10 min at 4°C. Sample was added to 0.8%
Two hours after endotoxin administration, rats displayed signs of acute endotoxemia, including piloerection and lethargy. Gross examination revealed hemorrhagic bowel; sanguine fluid in the lumen of the small intestine, cecum, and colon; and a granular appearance to the liver. These signs were absent in animals that received the optimal dose of pentostatin. Serum TNF-α was significantly elevated at 2 h post-LPS (Fig. 1). Pretreatment with pentostatin attenuated TNF-α concentrations in a dose-dependent manner, reaching a maximum attenuating effect at 0.1–0.5 mg/kg. This is 5- to 10-fold lower than a single-infusion pentostatin dose when used as an antineoplastic agent (4). It is important to note that pentostatin attenuated the concentrations of this proximal cytokine but was unable to ablate the response. LPS administration also resulted in significant elevation of serum IL-1β (Table 1). Pentostatin was able to attenuate IL-1 concentrations, similar to its effects on TNF-α. Both TNF-α and IL-1β were not detectable in serum from saline-challenged (non-LPS) rats, regardless of the presence or absence of pentostatin. Low concentrations of IL-10 were found in saline-challenged rats (82 ± 31 pg/ml). Significantly higher concentrations of IL-10 were measured 2 h after LPS administration (Table 1). Pentostatin had no effect on the IL-10 response to LPS at the doses that caused maximal attenuation of TNF-α and IL-1β, suggesting that the suppression of proinflammatory cytokines by pentostatin was not secondary to stimulation of this anti-inflammatory cytokine. However, examination of IL-10 concentrations in the liver and spleen revealed some further elevation in LPS-induced IL-10 after treatment with pentostatin. Gross appearance in pentostatin-treated LPS rats was indistinguishable from that of saline-challenged rats. Serum TNF-α and IL-1β were below detection of the assays in saline-challenged rats.

The effects of pentostatin on serum TNF-α in response to a much lower dose of LPS were investigated as well. The results are shown in Fig. 2. Administration of 0.01 mg/kg ip LPS resulted in elevated serum TNF-α, but this was significantly lower than that seen in response to 2 mg/kg LPS. Neither 0.5 nor 1.0 mg/kg pentostatin administration reduced serum TNF any
lower than it had when the higher dose of endotoxin was used (P = 0.94 and 0.901, respectively), suggesting a lower limit to the ability of pentostatin to attenuate this TNF response. Relative to untreated endotoxic rats, pentostatin resulted in a diminished response that did not achieve α-criteria for significance (P = 0.21) but had a power equal to 0.14, suggesting some true diminution of a much smaller magnitude.

**Chronic Sepsis**

We used a model of sepsis previously employed by our laboratory to study the role of endogenous adenosine in modulating the cytokine response to a more clinically relevant challenge. This model results in a hyperdynamic state within 24 h of sepsis induction (34, 36) and a progressive sepsis beyond day 3, with progressive leukocytosis and lactacidemia through day 7 (25). As shown in Table 2, serum TNF-α was elevated as early as 30 min after sepsis induction and remained elevated up to 72 h after sepsis induction. In liver and spleen, soluble TNF-α was also elevated at 24 h after sepsis induction (84.2 ± 10.8 and 63.8 ± 21.2 ng/g tissue, respectively). The surgical procedure (nonseptic controls) used to induce sepsis also resulted in a transient elevation of TNF-α in both liver (18.4 ± 5.3 ng/g) and spleen (9.3 ± 3.8 ng/g) at 24 h, but these were significantly lower than that in the septic rats.

The influence of endogenous adenosine on the 4- and 24-h serum TNF-α response to the septic challenge was determined in response to either pentostatin or 8-SPT. In the water-treated septic group, serum TNF-α was elevated at 4 and 24 h (Fig. 3), similar to that seen in Table 2. Pentostatin attenuated this response at both 4 and 24 h after sepsis induction. 8-SPT treatment resulted in significantly higher serum TNF-α at 24 h; at 4 h, the power of the comparison was too low to definitively state a difference, or lack thereof, but the direction of change was consistent with the 24-h effect. Similar results were found in liver and spleen total TNF-α at 24 h after sepsis induction (Fig. 4). These results indicate that preventing endogenous adenosine degradation with pentostatin diminishes the in vivo TNF-α response to sepsis, whereas blockade of adenosine receptors alone amplifies this response. These data are consistent with the hypothesis that endogenous adenosine is an important endogenous modulator of the proximal cytokine response to a septic challenge.

As a consequence of these effects of adenosine, we also postulated a modulation of oxyradical-mediated damage. Samples of liver and spleen were tested for evidence of TBARS resulting from the peritonitis. Liver and spleen TBARS in each group are shown in

![Graph showing serum TNF-α levels](image)

**Table 2. Serum tumor necrosis factor-α (pg/ml) at various times after induction of septic peritonitis using cecal slurry**

<table>
<thead>
<tr>
<th>Hours After Sepsis Induction</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>4.0</th>
<th>24</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=4)</td>
<td></td>
<td></td>
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<tr>
<td>83 ± 257</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Sepsis (n=6)</td>
<td>506 ± 173</td>
<td>1,927 ± 611</td>
<td>2,788 ± 406</td>
<td>1,369 ± 280</td>
<td>1,920 ± 342</td>
<td>650 ± 45</td>
</tr>
</tbody>
</table>

Values are means ± SE in pg/ml. ND, below the ability to detect.
In septic rats treated with 8-SPT, the concentration of tissue TBARS was increased in the spleen relative to that in the water-treated septic rat group. Liver values were also consistently elevated, albeit not to a statistically significant level. Pretreatment with pentostatin significantly reduced the tissue concentrations of TBARS relative to that in the water control-treated septic rats and 8-SPT-treated septic rats. These data indicate that endogenous adenosine is also an important modulator of oxyradical damage after a septic challenge.

Whereas the previous protocol was designed to assess effects of pentostatin on blood and tissue parameters while minimizing the confounding influence of examining only survivors, a more lethal challenge was used to study mortality per se. The survival data presented in Table 3 demonstrate the effectiveness of pentostatin in reducing mortality, even when it is administered 2 h after a more lethal septic challenge. One and six days after sepsis induction, 4 of 13 and 7 of 13 rats, respectively, had died in the vehicle-treated group. In contrast, only 1 of 13 rats in the pentostatin-treated group died (significantly different by Fisher's exact test: \( P = 0.03 \) at 6 days).

**DISCUSSION**

The data from these experiments compliment previous work from our laboratory (23, 24, 34, 36) and demonstrate a significant role for endogenous adenosine as a modulating component in SIRS. The results demonstrate that prevention of adenosine degradation attenuates proinflammatory cytokine responses after either LPS or a septic challenge, but a robust response remains intact. Blockade of adenosine receptors had the opposite effect, amplifying the elevation in TNF-\( \alpha \). As such, this modulation of proinflammatory cytokines can be directly associated with adenosine receptor-mediated actions and indicates that endogenously produced adenosine is modulating the response intermediate to either 8-SPT or pentostatin that was seen in the untreated LPS or septic rats. Importantly, beneficial effects of pentostatin use were not limited to pretreatment. Septic rats treated with 1 mg/kg pentostatin 2 h after sepsis induction were very well protected up to 6 days after the insult. These data indicate that endogenous adenosine is an important modulator of the responses to inflammatory processes. Furthermore, these data suggest that endogenous adenosine should not be considered an anticytokine molecule. Pentostatin had no significant effect on the TNF-\( \alpha \) response to a milder LPS challenge of 0.01 mg/kg, and it appeared that there was a lower limit to which manipulation of endogenous adenosine could be used to influence TNF-\( \alpha \). This may make this a novel therapeutic approach in that a significant proinflammatory response is left intact.

Earlier attempts to explore this question left unresolved problems. Firestein et al. (12) reported the ability of GP-1–515 to inhibit the TNF-\( \alpha \) response to LPS and that this could be blocked by adenosine receptor...
antagonism. However, the adenosine receptor antagonist had no effect on the LPS response in the absence of GP-1–515, which seemed to suggest that naturally evolved endogenous adenosine was playing no role. However, some important differences between those studies and ours should be pointed out. First, GP-1–515 is structurally similar to adenosine, leaving open the possibility of direct receptor-mediated influences of the compound. Their data also differ from ours in that adenosine receptor antagonism, in the absence or presence of GP-1–515, had no effect on IL-1β responses to LPS. Our data extended beyond LPS responses into a clinically relevant model of sepsis. In this setting, our data clearly demonstrate the capability to amplify or diminish influences of endogenous adenosine on multiple responses to a septic challenge. We also demonstrate a lower limit to the influences of endogenous adenosine, which may also explain the mixed results seen by Firestein et al. (12). In a recent report, Martin et al. (20) demonstrated that plasma adenosine concentrations were elevated in patients with sepsis and that the increased concentrations correlated with the severity of the patients’ condition. Earlier work from our laboratory demonstrated that endogenous adenosine is also a significant modulator of resting vascular tone in sepsis. Combined with the findings from the experiments reported herein, the evidence indicates that adenosine is a modulator of multiple physiological responses to inflammatory processes, strongly influencing, but not mediating, the clinical picture of SIRS. A summary hypothesis diagram of the proposed multiple modulatory functions of endogenous adenosine in SIRS is shown in Fig. 6.

Manipulation of adenosine’s metabolic pathways has been a therapeutic approach in the treatment of diseases such as myocardial ischemia and hairy cell leukemia (4). With the findings from our experiments and others, there is considerable evidence that manipula-

![Diagram of adenosine modulatory functions in SIRS](http://ajpregu.physiology.org/iраф/6329.png)
Inhibition of Adenosine Deaminase to Manage SIRS

The manipulation of adenosine metabolism could be beneficial in sepsis. Our manipulation of adenosine activity to affect the pathophysiology of septic insults reveals a self-limiting modulatory effect. The inability to suppress serum TNF-α below a limit, regardless of the severity of the challenge (Fig. 2), suggests that endogenous adenosine becomes an important modulator only when stimulation of the inflammatory response exceeds a minimum level. These responses are similar to in vitro effects. Adenosine is capable of suppressing macrophage activation and limiting cytokine release (11, 21, 32, 33), which is a likely source of the effects we are reporting herein. Adenosine also attenuates neutrophil adherence and production of reactive oxygen radical moieties by neutrophils (7, 8).

One of the most intriguing potentials in manipulating the adenosine pathway is that it would only dampen these responses, rather than resulting in total blockade or inhibition of these immune responses. This would allow for a more tempered response, which appears to be critical for survival (29). This is reminiscent of endogenous adenosine’s role as a negative feedback inhibitor of cardiac inotropic responses to stimulators of adenylyl cyclase (16). Adenosine is also a potent vasodilator, active only at sites of its production, where decreases in the oxygen supply-to-demand ratio prevail or where excessive adenylyl cyclase activity occurs. Even in this regard, manipulation of the adenosine metabolic pathway would only affect regions wherein endogenous adenosine is being produced in significant quantities and would have no effect in other regions. Such an approach is worth investigating for the treatment and management of sepsis. The fundamental premise for such an approach is that there are sufficient increases in endogenous adenosine production in relevant physiological systems during sepsis to render manipulation of adenosine’s metabolism effective for the treatment of clinical sepsis. The results presented herein attest to the validity of that premise.

We focused our attention primarily on changes in tissue and plasma TNF-α concentrations as a marker of the proximal cytokine response. TNF-α is the most thoroughly studied cytokine with regard to modulation by adenosine (2, 8, 11–13, 19, 27, 32). In addition, TNF-α is a proximal cytokine, initiating inflammatory responses to infection. However, the results of our studies in LPS-challenged rats indicate that endogenous adenosine can also play a role as modulator of other proximal proinflammatory cytokines, such as IL-1β. Pentostatin treatment also resulted in elevated liver and spleen IL-10 after LPS in vivo, which supports a role for this anti-inflammatory cytokine in these responses as well. Haskó et al. (13) reported that adenosine-mediated attenuation of macrophage proinflammatory responses could be explained, in part, by adenosine-mediated stimulation of IL-10. Such a cytokine interaction may be at work in the setting of SIRS. Further work is needed to determine how manipulation of endogenous adenosine pathways affects the mechanisms underlying inflammatory processes and cytokine interactions in SIRS responses.

Adenosine has also been shown to inhibit a variety of neutrophil functions, including adherence (7), TNF-stimulated lactoferrin secretion (31), and, importantly, H2O2 production (7). Oxyradical injury can also be a result of adenosine accumulation (1, 5, 6, 18, 22, 28, 37–39). Via either of these pathways, manipulation of endogenous adenosine pathways can influence net oxyradical-mediated damage. Our results support this, but the data cannot be used to determine the relative contribution of the pathways involved. The blockade of adenosine receptors could exacerbate oxyradical-mediated damage by preventing adenosine-mediated inhibition of neutrophil activity (7) or by reducing perfusion (23, 24, 34, 36). Reduction of oxyradical damage by preventing the degradation of endogenous adenosine could occur via increased inhibition of neutrophil activity and by preventing adenosine’s entry into the xanthine oxidase pathway. More work is needed to identify the relative contributions of each pathway that could be involved in these responses. Still, the data indicate that inhibition of the adenosine deaminase enzymes is also beneficial in the setting of sepsis in decreasing lipid peroxidation.

Therapeutic implications of these results are being explored. Endogenous adenosine’s immunomodulating actions behave as a physiological negative feedback system. As such, manipulation of adenosine pathways and receptor-mediated actions act via amplification or attenuation of complex physiological effector systems rather than the more conventional approaches that served to intervene directly on specific effector mediators. Thus physiological regulatory systems remain intact and active; inhibition of adenosine deaminase enzymes still allows for a robust immune response. Because sepsis is associated with an exaggerated immune response, tissue perfusion maldistribution, oxyradical-mediated tissue damage, and manipulation of adenosine deaminase hold therapeutic promise via modulation of all of these pathways in which endogenous adenosine serves as a physiological feedback mechanism.

Perspectives

Significant advances in our understanding of SIRS reveal a complex, multisystem pathology. SIRS have eluded significant advances in treatment, in part, as a result of its influences on diverse, yet integrated, phys-

Table 3. Survival

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Days After Sepsis (Sham) Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vehicle (9/13(69%))</td>
<td>6/13(46%)</td>
</tr>
<tr>
<td>Pentostatin (12/13(92%))</td>
<td>12/13(92%)</td>
</tr>
<tr>
<td>Sham (nonsespic) (6/6(100%))</td>
<td>6/6(100%)</td>
</tr>
</tbody>
</table>

Survival at 1 and 6 days after sepsis (or sham) induction indicated by no. of animals alive/total and percent surviving (in parentheses). Pentostatin (1 mg/kg) was administered intravenously 2 h after sepsis induction. *Significantly greater survival compared with vehicle-treated septic rats (P = 0.03).
iologic systems. The approach to managing SIRS reported herein, manipulating endogenous adenosine, is novel from two perspectives. First, the goal is to amplify normal physiological responses, those that occur via endogenously produced adenosine, to regain homeostasis. This differs from past approaches that target a single inflammatory molecule or second-messenger system in an attempt to directly influence outcome. Second, the approach influences diverse, yet integrated, physiological systems. Specifically, endogenous adenosine modulates local tissue perfusion, responses to inflammatory agents and inflammatory molecule interactions, oxyradical production via multiple pathways, and neurohumoral function, to name a few. These functions are accomplished through the various signaling pathways coupled to adenosine receptors in each cell type.

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