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Extracellular purines, including adenosine and ATP, are potent endogenous immunomodulatory molecules. Inosine, a degradation product of these purines, can reach high concentrations in the extracellular space under conditions associated with cellular metabolic stress such as inflammation or ischemia. In the present study, we investigated whether extracellular inosine can affect inflammatory/immune processes. In immunostimulated macrophages and spleen cells, inosine potently inhibited the production of the proinflammatory cytokines TNF-α, IL-1, IL-12, macrophage-inflammatory protein-1α, and IFN-γ, but failed to alter the production of the anti-inflammatory cytokine IL-10. The effect of inosine did not require cellular uptake by nucleoside transporters and was partially reversed by blockade of adenosine A1 and A2 receptors. Inosine inhibited cytokine production by a posttranscriptional mechanism. The activity of inosine was independent of activation of the p38 and p42/p44 mitogen-activated protein kinases, the phosphorylation of the c-Jun terminal kinase, the degradation of inhibitory factor kB, and elevation of intracellular cAMP. Inosine suppressed proinflammatory cytokine production and mortality in a mouse endotoxemic model. Taken together, inosine has multiple anti-inflammatory effects. These findings, coupled with the fact that inosine has very low toxicity, suggest that this agent may be useful in the treatment of inflammatory/ischemic diseases. The Journal of Immunology, 2000, 164: 1013–1019.

It is well recognized that certain naturally occurring purines can exert powerful effects on the immune system. The nucleoside adenosine is the best characterized of these purines, as both extracellular and intracellular adenosine have been shown to affect almost all aspects of an immune response (1–3). Adenosine and its analogues can alter the course of a variety of immune-mediated/infammatory diseases such as endotoxin shock (4, 5), rheumatoid arthritis (6, 7), pleural inflammation (8), nephritis (9), or uveitis (10). Adenosine is also recognized as one of the most important endogenous molecules able to prevent tissue injury in ischemia-reperfusion (11). Its effect is partly mediated by the inhibition of deleterious immune-mediated processes, including the release of proinflammatory cytokines and free radicals (11). Inosine is another endogenous purine nucleoside, which is formed during the breakdown of adenosine by adenosine deaminase (12). This molecule is released into the extracellular space from cells upon metabolic stress (13–15) or from the sympathetic nervous system (16). In ischemic tissues, inosine concentration may increase to levels as high as 1–3 mM (17), and increased inosine levels are present in various inflammatory states (18–20).

Cytokines are a heterogeneous group of hormone-like proteins, produced by all organs and many cell types of the body that establish a communication network between various cells of each organ. In inflammatory diseases and ischemic processes, large amounts of cytokines are produced, causing edema, cellular metabolic stress, and finally tissue necrosis. The proinflammatory cytokines TNF-α, IL-1, IL-12, macrophage-inflammatory protein (MIP)-1α, MIP-2, and IFN-γ are primarily involved in promoting inflammatory processes, and they also play an important role in ischemia-reperfusion injury (21–26). On the other hand, IL-10 is an anti-inflammatory cytokine that decreases inflammation and also has protective effects in ischemic processes (26, 27). Because of the important role of an altered cytokine balance in inflammatory/ischemic tissue injury, it is important to identify endogenously released molecules that are capable of restoring the normal equilibrium of pro- and anti-inflammatory mediators. In the present study, we demonstrate that inosine has the ability to prevent overproduction of proinflammatory cytokines, while it can enhance the production of the protective IL-10. We also show that the beneficial effects of inosine on cytokine production translate into a protective effect in an animal model of systemic inflammation/ischemia.

Materials and Methods

Mice

Male BALB/c mice (8 wk) were purchased from Charles River Laboratories (Wilmington, MA).

Reagents and drugs

LPS (from Escherichia coli, serotype O55:B5), inosine, monophosphate, hypoxanthine, thioglycolate medium, MTT, and pertussis toxin were purchased from Sigma Chemical Co. (St. Louis, MO). NBTI, 3-7-dimethyl-1-propargylxanthine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; 1-xB, inhibitor factor xB; JNK, c-Jun N-terminal protein kinase; MAPK, mitogen-activated protein kinase; NBTI, S-(4-nitrobenzyl)-6-thioguanosine.

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purchased from Sigma (St. Louis, MO). The selective A₁ receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), A₂a receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX), 3-isobutyl-1-methylxanthine, protein kinase inhibitor (5-24), dipyridamole, and S-(4-nitrobenzyl)-6-thioinosine (NBTH) were obtained from Research Biochemicals (Natick, MA). RPMI 1640, FCS, and penicillin-streptomycin were obtained from Life Technologies (Grand Island, NY). The mAb against mouse CD3 was obtained from Pharmingen (San Diego, CA).

Preparation and treatment of peritoneal macrophages

Mice were injected i.p. with 2 ml of 2% thioglycolate, and peritoneal cells were harvested 3 to 4 days later. The cells were plated on 96-well plastic plates at 1 million cells/ml and incubated in RPMI 1640 for 2 h at 37°C in a humidified 5% CO₂ incubator. Nonadherent cells were removed by rinsing the plates three times with 5% dextrose in PBS. Cells were treated with various concentrations of inosine, hypoxanthine, or inosine monophosphate 30 min before the addition of 10 μg/ml LPS for 24 h, and supernatants for cytokine and NO determination were taken at 24 h after LPS. For time course studies, inosine was added at various time points before or after LPS. Selective antagonists of adenosine receptors, dipyradomole, or pertussis toxin were added 30 min before inosine. Cytokines were determined by ELISA, as described below.

Preparation and treatment of spleen cell suspensions

Spleens from BALB/c mice were removed aseptically, and single spleen cell suspensions in RPMI 1640 were obtained by passage through a nylon mesh. RBC were lysed using Tris-NH₄Cl. Cells were cultured in 24-well plates at 5 million cells/ml and treated with inosine, followed by LPS (10 μg/ml) or anti-CD3 Ab (2 μg/ml) 30 min later for 5 days. The plates were then centrifuged and IFN-γ was measured from the supernatants by ELISA, as described below.

Cytokine assays

Cytokine concentrations in the supernatants were determined by ELISA kits that are specific against murine cytokines. Levels of TNF-α, IL-1, IL-10, IL-12, MIP-1α, MIP-1β, and IFN-γ were measured using ELISA kits purchased from Genzyme (Boston, MA) and R&D Systems (for MIP-1α and MIP-2; Minneapolis, MN). Plates were read at 450 nm by a Spectramax 250 microplate reader from Molecular Devices (Sunnyvale, CA). Detection limits were 5 pg/ml for TNF-α, 3 pg/ml for IL-1β, 0.15 pg/ml for IL-10, 10 pg/ml for IL-12 (total), 1.5 pg/ml for MIP-1α, 1.5 pg/ml for MIP-2, and 5 pg/ml for IFN-γ. Assays were performed according to the manufacturer’s instructions.

Western blot analysis

Cells in 6-well plates were pretreated with inosine or vehicle, and 30 min later the cells were stimulated with LPS (10 μg/ml) for various lengths of time (5–60 min). After washing with PBS, the cells were lysed by the addition of modified radioimmunoprecipitation buffer (50 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 0.25% Na-deoxycholate, 1% Nonidet P-40, 1 μg/ml pepstatin, 1 μg/ml leupeptin, 1 mM PMSF, 1 mM Na₃VO₄). The lysates were transferred to Eppendorf tubes and centrifuged at 15,000 × g, and the supernatant was recovered. Protein concentrations were determined using a Bio-Rad protein assay (Bio-Rad, Hercules, CA). The membranes were probed with anti-phospho-mitogen-activated protein kinase (MAPK; p42/p44), antiphospho-c-Jun N-terminal protein kinase (JNK; PKN: Promega, Madison, WI), anti-phospho-p38 MAPK (p38 MAPK; New England Biolabs, Beverly, MA), or an anti-I-kB (Upstate, Lake Placid, NY) Ab, and subsequently incubated with a secondary HRP-conjugated donkey anti-rabbit Ab (Boehringer, Indianapolis, IN). Bands were detected using ECL Western Blotting Detection Reagent (Amersham Life Science). The membranes were probed with an anti-phospho-nitrogen-activated protein kinase (MAPK; p42/p44), anti-phospho-c-Jun N-terminal protein kinase (JNK; PKN; Promega, Madison, WI), anti-phospho-p38 MAPK (p38 MAPK; New England Biolabs, Beverly, MA), or an anti-I-kB (Upstate, Lake Placid, NY) Ab, and subsequently incubated with a secondary HRP-conjugated donkey anti-rabbit Ab (Boehringer, Indianapolis, IN). Bands were detected using ECL Western Blotting Detection Reagent (Amersham Life Science).

RNA isolation and RNase protection assay

Cells in 6-well plates were treated the same way as in the case for cytokine protein measurements, and RNA was isolated 90 min after LPS treatment. Macrophage monolayers were washed with PBS and total cellular RNA was extracted from each well using a guanidinium isothiocyanate/chloroform-based technique (TRIZOL; Life Technologies), followed by isopropylalcohol precipitation. RNase protection assay was performed using a kit obtained from Pharmingen. Briefly, antisense RNA multiprobe set was synthesized by an in vitro transcription of a mouse cytokine template set using T7 RNA polymerase in the presence of [α-³²P]UTP (sp. act., 3000 Ci/mM; Amersham). The probe set (3 × 10⁷ cpm/ml) was hybridized with target RNA (10 μg) at 56°C overnight in a total of 10 μl of hybridization buffer. The free probe and single-stranded target RNA were digested with RNase at 30°C for 45 min. The proteins were digested by treating with proteinase K for 15 min at 37°C and extracted with phenol/chloroform:isoamyl alcohol (25:24:1). The aqueous phase was removed, and the protected RNA was precipitated with ethanol. The pellet was washed with 90% ethanol, air dried, and resuspended in 4 μl of loading buffer. The sample was then heated for 3 min at 90°C and separated on 6% sequencing gel (Novex). The gel was then vacuum dried, and exposed to x-ray film (Kodak) for 24 h at −70°C.

CAMP determination

Peritoneal macrophages in 6-well plates (1 million/well) were treated with inosine, isoproterenol, or vehicle in the presence of the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (200 μM) for 10 min. At the end of the incubation period, the cells were lysed using 0.1 N HCl (500 μl), scraped, and sonicated. CAMP content of the cell lysates was determined after acetylation of the samples using a low pH cAMP kit from R&D Systems.

Measurement of mitochondrial respiration

Mitochondrial respiration, an indicator of cell viability, was assessed by the mitochondria-dependent reduction of MTT to formazan (28). Cells in 96-well plates were incubated with MTT (0.5 mg/ml) for 60 min at 37°C. Culture medium was removed by aspiration, and cells were solubilized in DMSO (100 μl). The extent of reduction of MTT to formazan within cells was quantitated by measurement of OD at 550 nm using a SpectraMax 250 microplate reader.

In vivo studies

Animals were injected i.p. with drug vehicle (physiologic saline) or inosine (100 mg/kg) in a volume of 0.1 ml/10 g body weight. Thirty minutes later, they were challenged with 70 mg/kg of LPS administered i.p. The animals were bled at various time points after LPS treatment. Blood was collected in ice-cold Eppendorf tubes containing heparin and centrifuged for 10 min at 4°C. The plasma was stored at −70°C until assayed. Cytokines from the plasma were detected with ELISA, as described above. For lethality studies, the mice were injected i.p. with drug vehicle or inosine (as described above), followed by an i.p. LPS challenge (70 mg/kg) 30 min later. Survival was recorded 24 h, 48 h, 72 h, 96 h, and 2 wk after the LPS injection.

Statistical evaluation

Values in the figures, tables, and text are expressed as mean ± SEM of n observations. Statistical analysis of the data was performed by one-way ANOVA, followed by Dunnett’s test, as appropriate. Survival differences were evaluated with the χ² test.

Results

Effect of inosine on cytokine and chemokine production in LPS-stimulated peritoneal macrophages

First, we determined in vitro whether inosine can decrease the production of the proinflammatory cytokines, TNF-α, IL-1, and IL-12. As shown in Figs. 1 and 2, inosine pretreatment of peritoneal macrophages 30 min before LPS caused a dose-dependent suppression of the release of both TNF-α and IL-1, as well as IL-12. We next examined whether inosine can alter the production of the chemokines MIP-1α and MIP-2. Our results demonstrate that in LPS-induced peritoneal macrophages, inosine potently inhibits MIP-1α production, while it does not affect MIP-2 release (Fig. 2). Finally, we tested whether inosine has an effect on the production of IL-10. Fig. 1c shows that inosine failed to significantly alter the production of this cytokine (although a tendency toward an increase was apparent). Similarly, inosine failed to influence the production of the free radical NO (data not shown). Finally, inosine did not affect cellular viability in any of the experiments, as determined with the MTT assay or the trypan blue exclusion test (>99% as compared with untreated wells).
The effect of inosine is not sensitive to nucleoside uptake into cells and is partially mediated via adenosine receptors

Because TNF-α is one of the most multipotent cytokines and the effect of inosine on TNF-α was highly potent, this cytokine was chosen to study the mechanisms of the effect of inosine. First, we studied whether cellular uptake of inosine is necessary for its effect. To this end, we used dipyridamole, a selective blocker of nucleoside uptake. Although dipyridamole alone caused a substantial inhibition of TNF-α release (29), dipyridamole and inosine together additively suppressed the production of this cytokine, suggesting that the effect of inosine cannot be prevented by blockade of nucleoside uptake (Table I; inosine inhibited TNF-α by 72 ± 2% in the absence of dipyridamole and by 71 ± 3% in the presence of dipyridamole; p > 0.05). Similar results were obtained using another nucleoside uptake inhibitor, NBTI (not shown). Next, we examined whether the effect of inosine is sensitive to G protein inhibition by pertussis toxin. Although, similar to the finding of a previous study, pertussis toxin alone enhanced TNF-α production (30), the effect of inosine was similar in both the absence and presence of pertussis toxin (not shown). Because of structural similarities to adenosine, we surmised that the effect of inosine was mediated by an adenosine receptor. Both A1 and A2 antagonists alone augmented TNF-α production, suggesting that endogenous adenosine inhibits cytokine production (29). However, in the presence of both antagonists, the inhibition by inosine of TNF-α was significantly, although not completely, abrogated, suggesting that the effect of inosine is at least partially mediated via adenosine receptors.

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Besides adenosine, inosine monophosphate is another precursor of adenosine; therefore, we studied whether inosine monophosphate can affect TNF-α release. Inosine monophosphate also suppressed TNF-α production, however less potently than inosine.
(EC_{50} \approx 500 \mu M). Because inosine is degraded to hypoxanthine in murine peritoneal cells (12), we examined whether the effect of inosine is mediated by hypoxanthine. However, in contrast to inosine, hypoxanthine failed to alter TNF-\alpha release (not shown).

**Inosine fails to alter LPS-induced I-\kappa B degradation, MAPK, and JNK activation**

The p42/44 MAPK, p38 MAPK, and JNK are important intracellular components of the inflammatory responses to LPS (31, 32). Therefore, we tested whether the anti-inflammatory effect of inosine is due to interference with these pathways. Fig. 3 shows that the activation of these enzymes by LPS was not influenced by pretreatment with inosine. The degradation of I-\kappa B, the inhibitory part of the NF-\kappa B/I-\kappa B complex, is a central event in the transcriptional activation of a host of cytokine genes, including TNF-\alpha, IL-1, IL-12, MIP-1\alpha, and MIP-2 (33, 34). Although LPS induced the degradation of I-\kappa B at 15 min after stimulation, pretreatment with inosine did not change I-\kappa B degradation (Fig. 3). Because purinergic agents can increase intracellular levels of cAMP (35), and elevation of cAMP inhibits cytokine production (2), we determined whether inosine can alter intracellular cAMP levels. Although the \beta-adrenoceptor agonist isoproterenol caused a substantial increase in cAMP, inosine failed to exhibit such an effect (vehicle, 0.28 \pm 0.03 pmol/ml (n = 3); isoproterenol, 1.25 \pm 0.14 pmol/ml (n = 3); inosine, 0.25 \pm 0.09 pmol/ml (n = 3)). The lack of involvement of cAMP in the effect of inosine was confirmed in an experiment, in which cAMP-dependent protein kinase inhibitor (5–24) failed to reverse the inhibition of TNF-\alpha production by inosine (not shown).

**The effect of inosine on cytokine production is posttranscriptional**

Using RNase protection assay, we examined whether inosine can modify the expression of a host of cytokine mRNAs in LPS-stimulated macrophages. Although LPS induced a strong increase of mRNA levels of TNF-\alpha, MIP-1\alpha, MIP-2, RANTES, and TGF-\beta, inosine failed to suppress this response (Fig. 4a). Therefore, the effect of inosine on cytokine production is posttranscriptional. This finding was confirmed in a second set of experiments, in which inosine was added to the cells at various time points before and after the LPS challenge, and was able to inhibit TNF-\alpha production, even when added 1.5 h after LPS (Fig. 4b).

**Inosine suppresses the production of the Th1 cytokine IFN-\gamma**

Because IFN-\gamma produced by Th1 lymphocytes and NK cells is another important mediator in inflammatory/immune processes, we examined in spleen cells whether inosine modulates the release of this cytokine. Spleen cells (10 million/ml) obtained from BALB/c mice were treated with inosine, which was followed by the administration of either LPS or anti-CD3 Ab 30 min later for 4 days. IFN-\gamma levels were determined from the supernatants. Fig. 5 shows that IFN-\gamma production was suppressed by inosine in both the LPS- and anti-CD3-induced cells. Inosine failed to alter cellular viability in any of the experiments, as determined with the MTT assay.
Inosine exerts multiple anti-inflammatory effects in vivo

Based on the above in vitro data, we surmised that inosine can also influence the cytokine response in vivo. To test this hypothesis, we injected mice with inosine (100 mg/kg; i.p.), followed by an i.p. injection of LPS (70 mg/kg) 30 min later, and determined plasma levels of the different cytokines at selected time points (90 min, 2 h, 4 h, and 8 h) after the LPS challenge. Similar to its in vitro effect, inosine decreased plasma levels of TNF-α, IL-12, IFN-γ, and MIP-1α, while it augmented the production of IL-10 (Fig. 6). Furthermore, inosine also suppressed the production of IFN-γ, which is also involved in the proinflammatory effects of LPS. Taken together, inosine selectively and differentially alters the production of cytokines in vivo. Namely (1), it inhibits the production of proinflammatory cytokines, but (2) potentiates the formation of the anti-inflammatory IL-10.

Because inosine skewed the cytokine response toward an anti-inflammatory profile, we hypothesized that inosine would decrease LPS-induced lethality. To this end, we injected mice with inosine (100 mg/kg) 30 min before a lethal dose of LPS (70 mg/kg) and observed the animals for 2 wk. Fig. 7 shows that inosine conferred significant protection in this endotoxemic model.
Discussion

Inosine is considered an inactive metabolite in most biological systems; however, recent evidence indicates that extracellular inosine has powerful cellular protective effects. For example, it prevents glial cell death during glucose deprivation (36, 37), decreases the release of intracellular enzymes from hypoxic lymphocytes (38), improves renal function during ischemia (39, 40), and removes the harmful effects of total hepatic ischemia (41). Inosine administration has also been shown to improve myocardial function during acute left ventricular failure (42, 43) and decrease infarct size after coronary occlusion (44, 45). Despite the accumulating evidence of inosine’s protective effects, there is little information on the mode(s) of action of this metabolite in inflammatory/immune processes. In the current study, we presented evidence that inosine, but not its degradation product hypoxanthine, has multiple anti-inflammatory effects both in vitro and in vivo by decreasing the production of a host of proinflammatory mediators, including TNF-α, IL-1, IL-12, MIP-1α, and IFN-γ. Although the production of IL-10 was not affected by inosine in vitro, IL-10 production was clearly augmented in the in vivo endotoxic shock model. Such a differential regulation of IL-10 by endogenous anti-inflammatory molecules in vitro and in vivo is not unprecedented. For example, adenosine receptor agonists enhanced LPS-induced plasma IL-10 levels, but failed to enhance LPS-induced IL-10 production in vitro (28). The shift toward an anti-inflammatory cytokine profile (decrease in TNF-α, IL-1, IL-12, MIP-1α, and IFN-γ, and increase in IL-10) by inosine is in agreement with its beneficial effect in the endotoxic shock model. Furthermore, it can be suggested that the anti-ischemic effects of inosine can, at least partly, be due to its effect on cytokine production.

It is difficult to pinpoint the mode of action of inosine on the cellular level. Because nucleoside uptake inhibitors failed to reverse the effect of inosine on TNF-α production, it is conceivable that inosine is acting through a cell surface receptor. Conversely, the effect of inosine on the stimulation of axon outgrowth in neu- rons (46) or on the protection of glucose-oxygen-deprived astrocytes can be prevented by dipyridamole (36), suggesting an intracellular mechanism in these models. Recently, the group of Linden showed that inosine is able to bind and activate adenosine A₁ receptors in mast cells, resulting in degranulation (47). In our study, both A₁ and A₂ receptor antagonists partially reversed the effect of inosine, suggesting an adenosine receptor-mediated mechanism. It is possible that inosine produces its inhibitory effect on cytokines via binding to A₁ receptors, because monocytes/macrophages have been shown to express A₁ receptors (48, 49). Furthermore, stimulation of this receptor subtype suppresses proinflammatory cytokine production (5, 7, 48, 49). However, the lack of availability of receptor antagonists that are selective for the rodent A₁ receptor (50) makes it difficult to investigate the possible interaction of inosine with this receptor subtype.

The effect of inosine was posttranscriptional and did not involve interference with the activation of p38, p42/44, JNK, degradation of I-κB, or elevation of intracellular Ca²⁺ levels. It has recently been established that the production of proinflammatory cytokines can be regulated at the translational level. For example, tetracycline (51), chloroquine (52), metalloproteinase inhibitors (53), or polyamines (54) suppress the production of inflammatory mediators without affecting transcriptional events. Interestingly, inhibitors of the p38 MAPK act predominantly at the protein level to decrease cytokine production (55), and even the inhibition of cytokine production by glucocorticoids has a posttranscriptional component (56).

Inosine is used in the clinical practice for various forms of cardiovascular disorders including ischemic events (17), and isopronisine, a synthetic drug containing inosine, has antiarthritic (57) and antiviral effects (58). Based on our data, it can be suggested that the decrease in proinflammatory mediators can contribute to the beneficial effects of these agents in human disease. The posttranscriptional nature of inosine’s mechanism of action can be considered as preferable to transcriptional inhibitors, because it is expected to increase the window of therapeutic opportunity, and may remain effective even in a posttreatment paradigm. Several drugs used in the treatment of autoimmune and inflammatory diseases, including adenosine kinase inhibitors (59), methotrexate (60), sulfasalazine (61), or aspirine (62), have been proposed to exert their beneficial effects by releasing adenosine. Because adenosine is readily degraded to inosine in the extracellular space, it is conceivable that this metabolite is also involved in the anti-inflammatory effects of these adenosine-releasing agents.

References


