Amphotericin B Activation of Human Genes Encoding for Cytokines

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Amphotericin B has been shown to cause release of cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), from monocytes and macrophages. Human and murine monocytic cell lines were used to evaluate the effects of amphotericin B on the transcription of IL-1α, IL-1β, and TNF-α and the transcription and production of soluble IL-1 receptor antagonist (sIL-1Ra). The effects of inhibitors of transcription and translation on amphotericin B-induced IL-1β expression in a human monocytic cell line were also evaluated. Amphotericin B markedly increased IL-1β and TNF-α mRNA levels, with peak levels occurring by 4 h. Amphotericin B induced production of sIL-1Ra in a dose-dependent fashion and induced sIL-1Ra mRNA, with peak levels at 24 h. Cycloheximide and actinomycin D resulted in a dose-dependent decrease in amphotericin B-induced IL-1β expression at 2 h. Thus, amphotericin B induces gene expression for IL-1β, TNF-α, and IL-1Ra in human and murine monocytic cells.

Amphotericin B is an intravenously administered polyene antifungal agent used in the treatment of severe fungal infections. Its use is limited, however, by a number of adverse drug reactions (ADRs). These ADRs include dose-dependent nephrotoxicity, with secondary anemia, hypokalemia, hypomagnesemia, and cardiac arrhythmias, as well as infusion-related fever, chills, hypotension, and nausea. Infusion-related ADRs are observed in as many as 70% of patients who receive the drug [1]. On the basis of in vitro laboratory and in vivo clinical studies, these infusion-related ADRs appear to involve the release of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) from monocytes and prostaglandin E2 from monocytes and endothelial cells [2–6]. It has been suggested that IL-1 may be the most important of the cytokines involved in amphotericin B–associated acute infusion-related reactions [3, 4].

IL-1 is an inflammatory cytokine that affects many different cell types and elicits pleiotropic effects. Enhanced IL-1 expression has been observed in numerous disease states, including endotoxic shock. It actually comprises two unique proteins (IL-1α and IL-1β) derived from two different but related genes. Both proteins are expressed as a 31-kDa precursor that is cleaved to the active mature 17-kDa protein by cellular proteases. IL-1β is cleaved by a specific cysteine protease, IL-1–converting enzyme (or caspase-1), but its mechanism of secretion is atypical and poorly understood [7–9]. TNF-α is a 17-kDa protein produced by monocytic cells and is one of the primary mediators of endotoxic shock and inflammation [10–12].

Lipopolysaccharide (LPS) has been shown to elicit IL-1β and TNF-α expression from human monocytic cells [10]. Amphotericin B infusion–related reactions are qualitatively similar to but milder than those observed with septic shock secondary to LPS from gram-negative aerobic bacteria. Previous studies have demonstrated increased expression of IL-1β and TNF-α in monocytes in vitro and in the serum of patients treated with amphotericin B [3–5, 13].

The endotoxin-like hypotension and fever induced by amphotericin B occur within 60–180 min of drug administration [1]. Physiologically significant amounts of these cytokines are produced in this time frame with in vivo amphotericin B infusion or in vitro from amphotericin B stimulation of monocytes [3–5, 13–15]. To our knowledge, the mechanism of amphotericin B–induced proinflammatory cytokine secretion has not been investigated, nor has it been demonstrated that transcription of these proinflammatory cytokine genes occurs. The observed protein expression could be due to release of preformed protein by the effects of amphotericin B on the phagocytic cell membrane. With the exception of IL-6, other proinflammatory factors, as well as the primary modulators of the biologic effects of these cytokines in vivo, have not been thoroughly examined. The heterogeneity of amphotericin B infusion–related ADRs, their variable occurrence, and their self-limited nature may be due to variation in these other “regu-
latory” molecules, which likely include the novel interleukin-1 receptor antagonist (IL-1Ra) or soluble TNF and IL-1 receptors.

Previously, our laboratory has demonstrated that amphotericin B induces secretion of increasing concentrations of IL-1β over time, with maximal concentrations observed at ~10 h after exposure [3]. This work and work by others led us to hypothesize that amphotericin B induces transcription of mononuclear cell genes that encode for inflammatory cytokines and that these events occur within the time frame of observed amphotericin B infusion–related reactions. In addition, we also proposed to measure the secreted interleukin-1 receptor antagonist (sIL-1Ra) gene transcription and protein expression to determine whether sufficiently high levels are released to inhibit the biologic effects of IL-1β. We hypothesized that IL-1Ra production occurs in a more delayed fashion than does IL-1β production, suggesting that it may limit systemic amphotericin B infusion–related reactions.

Materials and Methods

Reagents. RPMI 1640 medium was obtained from Sigma (St. Louis). Low-endotoxin fetal bovine serum was purchased from Summit Biotech (Fort Collins, CO) and Life Technologies Gibco (Grand Island, NY). The stimulators of protein expression used in this study included amphotericin B (Fungizone; Squibb, Princeton, NJ) and Escherichia coli endotoxin (LPS; serotype O26:B6; Sigma). Inhibitors of protein expression included actinomycin D (lot 95H4001; Sigma) and cycloheximide (lot 16H1483; Sigma). Plasmids and cell lines were purchased from the American Type Culture Collection (Rockville, MD). Restriction endonucleases and serum supplements were obtained from Gibco.

All media, media supplements, and reagents used in tissue culture, including amphotericin B, were assayed for endotoxin contamination by the gel clot method used by the Limulus amebocyte lysate (LAL) assay (Associates of Cape Cod, Woods Hole, MA). LAL assay sensitivity was 0.03 EU/mL (3.25–20.0 pg/mL of E. coli endotoxin standard). All media and reagents as well as media incubated in cell-free culture plates tested negative for endotoxin contamination at this level. All reagents tested negative for endotoxin at concentrations between 100-fold and 0.01-fold that used in tissue culture. The sensitivity of the endotoxin assay was not changed when amphotericin B, up to 100 μg/mL, was added to the endotoxin standard. However, inhibition of the LAL gel clot assay at concentrations >5 mg/mL amphotericin B were noted.

Cell culture. The human mononuclear cell line THP-1 (ATCC TIB 202) was cultured in RPMI 1640 medium supplemented with 10% fetal calf serum, 2 × 10⁻⁵ M β-mercaptoethanol, 2 mM L-glutamine, 100 U/mL penicillin, and 100 mg/mL streptomycin (complete media). The cells were cultured in suspension at 37°C and 5% CO₂ in a humidified incubator and carried at 0.1–2.0 × 10⁶ cells/mL, passing two to three times weekly as needed. In selected studies, the murine mononuclear cell line RAW 264.7 (ATCC TIB 71) was cultured under similar conditions.

Cells were pelleted and resuspended in fresh complete media in tissue culture plates (WVR Scientific, Sugarland, TX) 24 h before use in experiments to avoid any confounding gene expression that might occur because of handling. Amphotericin B concentrations >10 μg/mL have previously been noted to be associated with low cell viability [3]. Therefore, amphotericin B concentrations between 0.25 and 5 μg/mL were used, corresponding to pharmacologically achievable levels in most patients. Stimuli (amphotericin B and LPS) and inhibitors (actinomycin D and cycloheximide) were resuspended in endotoxin-free water at an appropriate stock concentration and stored in aliquots at −20°C. Stock concentrations were used that allowed addition of stimuli to tissue culture cells with a change in volume of <1%.

Protein assays. IL-1β and sIL-1Ra concentrations were determined with commercial ELISA kits. After stimulation, cell-free THP-1 culture supernatants were subjected to three quick freeze-thaw cycles, clarified by microcentrifugation [16], and stored at −70°C until assayed. Samples were assayed for IL-1β (Cistron Biotechnology, Pine Brook, NJ) in triplicate. Samples were assayed for sIL-1Ra by ELISA (R&D Systems, Minneapolis) in duplicate at a 1:4 or 1:10 dilution. Both assays are specific sandwich-type ELISAs that do not cross-react with other members of the IL-1 family or other cytokines. Manufacturers’ data indicate an assay sensitivity of 4.0 pg/mL for IL-1β and at least 22 pg/mL for IL-1Ra.

RNA preparation. For Northern and slot blot analysis, total cellular RNA was harvested from 1.5 × 10⁷ cells cultured at 1×10³ cells/mL in T-75 tissue culture flasks (Sarstedt, Newton, NC). In other experiments, total cellular RNA for reverse transcription–polymerase chain reaction (RT-PCR) was harvested from 5 × 10⁶ cells cultured at 0.5×10³ cells/mL in 100-mm plates (Fisher Scientific, Pittsburgh). For Northern and slot blot analysis, total cellular RNA was isolated by a modification of a previously described single-step method using guanidinium lysis followed by phenol-chloroform extraction and treatment with DNase H to eliminate genomic DNA contamination [17]. For RT-PCR, total cellular RNA was isolated by guanidinium isothiocyanate lysis and centrifugation through a CsCl cushion as previously described [18]. After preparation, the RNA was washed in 70% ethanol, pelleted, dried, and resuspended in RNase-free water. Isolation of intact total cellular RNA was verified by gel electrophoresis of a small aliquot, staining with 1% ethidium, and visualization under UV light. The concentration and purity were determined by spectrophotometry. The techniques yielded similar quantities and purity of RNA from cell cultures.

Northern and slot blot analysis. Northern and slot blot analysis was done on RNA extracted from THP-1 cells stimulated with amphotericin B or LPS and also cells cultured only in complete medium. Northern blot analysis followed a standard protocol. Briefly, equal amounts of total cellular RNA were electrophoresed on a formaldehyde-containing agarose gel. The RNA was then transferred to a nitrocellulose membrane by capillary blotting, air-dried, and cross-linked with 12,000 μJ of 254-nm UV short-wave light (UVC-515 Ultraviolet Multilinker; Ultra Lumin, Paramount, CA). For slot blots, equal amounts of RNA were transferred to a membrane through a slot blot apparatus and cross-linked similarly.

The 606-bp BamHI/SmaI insert in the 8.97-kb Yepsec1 plasmid (ATCC 67024) was used as a probe for IL-1β. This fragment se-
Amphotericin B induces IL-1β and TNF-α mRNA. Other reports have indicated that amphotericin B in vitro and in vivo causes release of IL-1β and TNF-α protein [2–6]. To examine whether amphotericin B induced IL-1β or TNF-α mRNA, THP-1 cells were stimulated with 5 μg/mL amphotericin B. Unstimulated cells (cultured in complete medium only) and LPS-stimulated (0.1 μg/mL) cells were used as negative and positive controls, respectively. Viability of THP-1 cells did not differ from control under any experimental condition.

At 6 h, RNA was harvested and analyzed by Northern or slot blot. Figure 1 shows that amphotericin B (lane 2) induced a moderate amount of IL-1β mRNA compared with that induced by the strong stimulus LPS (lane 1). Band intensity per pixel was 132 ± 3 bipps for amphotericin B, compared with...
Figure 3. Effect of amphotericin B (AmB; 0.25 and 1 μg/mL) and lipopolysaccharide (LPS; 0.1 μg/mL) on interleukin (IL)-1 receptor antagonist (Ra) expression in THP-1 cells at 24 and 48 h.

407 ± 9 bipps for LPS and 25 ± 4 bipps for media control (lane 3). The amphotericin B–induced signal is ~5-fold the control. Slot blot analysis using a TNF-α probe is shown in figure 2. At 6 h, amphotericin B– (lane 2) and LPS-induced (lane 1) TNF-α mRNA appear similar in magnitude and are ~6-fold the control in lane 3 (band intensity values: LPS, 200 ± 3 bipps; amphotericin B, 200 ± 6 bipps). In experiments incubated for <6 h, bands from amphotericin B were difficult to discriminate from negative controls. We believe that the sensitivity of the blot technique was responsible for this outcome.

Amphotericin B induces sIL-1Ra protein. Because IL-1β has been suggested to be a key mediator of amphotericin B infusion–related ADRs, we examined whether amphotericin B also induced one of the primary modifiers of IL-1 biologic effects, sIL-1Ra. In addition, monocyte production of this molecule is induced by many of the same stimuli (including LPS) as IL-1. We measured IL-1Ra protein production in supernatants of THP-1 cells cultured at /mL in 1 mL and stimulated with 0.25 or 1 μg/mL amphotericin B for 24 and 48 h (n = 6). Unstimulated and LPS-stimulated (0.1 μg/mL) cells served as negative and positive controls, respectively.

Unstimulated cells had 1300 ± 220 pg/mL and 870 ± 220 pg/mL IL-1Ra protein at 24 and 48 h, respectively (figure 3). As previously described in monocytes, LPS induced large amounts of IL-1Ra protein, 7760 ± 1900 pg/mL at 24 h and 28,040 ± 3910 pg/mL at 48 h. Amphotericin B–stimulated THP-1 cells also produced large amounts of supernatant IL-1Ra in a dose- and time-dependent manner. When stimulated with 0.25 μg/mL amphotericin B, THP-1 cells produced 4260 ± 1780 pg/mL and 5350 ± 1830 pg/mL IL-1Ra, and with 1.0 μg/mL amphotericin B, they produced 5330 ± 1700 pg/mL and 11,880 ± 3280 pg/mL IL-1Ra protein at 24 and 48 h, respectively. Amphotericin B–induced IL-1Ra was then further examined in RT-PCR studies.

RT-PCR of amphotericin B–stimulated THP-1 cells for IL-1β, TNF-α, and sIL-1Ra. Amphotericin B–induced IL-1β, TNF-α, IL-1α, and sIL-1Ra mRNA were examined at various times after stimulation by semiquantitative RT-PCR and compared with results of LPS (0.1 μg/mL) and media stimulation. THP-1 cells (5 × 10⁵) in 10 mL were stimulated with 5 μg/mL amphotericin B. Figure 4 illustrates the RT-PCR IL-1β results after stimulation for up to 6 h for LPS and 24 h for amphotericin B. The lower band represents the uniformly amplified internal control, GAPDH, and the upper band, IL-1β. No IL-1β mRNA was detected in unstimulated cells at 0, 4, and 24 h. IL-1β mRNA became detectable in amphotericin B–stimulated cells at 0.5 h, increased to 4 h (peak), and diminished progressively thereafter. Compared with LPS, amphotericin B induced lower peak levels of IL-1β mRNA at similar times after stimulation. Similar amphotericin B–induced IL-1β mRNA levels were observed in RAW 264.7 murine macrophages (data not shown). IL-1α mRNA was not amplified significantly in amphotericin B– or LPS-stimulated THP-1 cells with 30 PCR cycles at all time points evaluated (not shown).

Levels of TNF-α mRNA were examined in a similar fashion. In figure 5, amplified TNF-α was barely detectable in unstimulated cells at 2 h but undetectable at 0, 4, 6, and 24 h (24 h not shown). Amphotericin B induced peak levels at 2 h, which then declined progressively from 6 h to 24 h (24 h not shown). In contrast, LPS induced peak levels at 1 h, which declined rapidly thereafter. TNF-α mRNA levels were barely detectable at 24 h with either stimulus (not shown) at 25 cycles. Similar amphotericin B–induced TNF-α mRNA levels were observed.

Figure 4. Effect of media (at 0, 4, and 24 h), lipopolysaccharide (LPS, 0.1 μg/mL, at 0.5, 1, 4, and 6 h), and amphotericin B (AmB, 5 μg/mL, at 0.5, 1, 4, 6, and 24 h), on interleukin-1β mRNA expression in THP-1 cells.
in RAW 264.7 murine macrophages (data not shown). In another experiment, Northern analysis of TNF-α mRNA verified that peak amphotericin B–induced levels occurred at 4 h.

In figure 6, no detectable sIL-1Ra mRNA was amplified in unstimulated cells at 0, 4, or 24 h. Amphotericin B induced peak sIL-1Ra mRNA at 24 h. Although amphotericin B induced less sIL-1Ra mRNA than did LPS, the kinetic profile was similar.

Effect of transcriptional and translational inhibitors on IL-1β protein expression. The previous data suggest that transcription of the IL-1β gene is required for amphotericin B to produce measurable supernatant IL-1β protein. The knowledge that pro–IL-1β may exist in monocytes, that amphotericin B may induce membrane perturbations, and that monocytes may be easily stimulated by physical phenomena prompted us to further explore the mechanism of amphotericin B–induced cytokine expression. We examined the effects of inhibitors of translation and transcription on amphotericin B–induced IL-1β. In studies using actinomycin D and cycloheximide, cells were exposed to these agents for 2 h before amphotericin B stimulation. Cycloheximide and actinomycin D were observed to have a detrimental effect on cell viability with 24 h of exposure.

THP-1 cells in complete media were treated with various concentrations of the inhibitors immediately before stimulation with amphotericin B, and supernatants were harvested for IL-1β protein measurement. Actinomycin D (0.01–100 mg/mL) and cycloheximide (0.1–1000 mg/mL) were added to cultures to inhibit transcription and translation, respectively. After only 2 h, actinomycin D– and cycloheximide-treated cultures had significantly less IL-1β than did amphotericin B–stimulated cultures (figure 7). The inhibition of amphotericin B–induced IL-1β occurred in a dose-dependent fashion and was present at concentrations as low as 0.1 mg/mL actinomycin D and 0.1 mg/mL cycloheximide. Erythrosin B exclusion in these experiments demonstrated no significant change in cell death that could account for the reduction in IL-1β between cultures receiving amphotericin B alone and those receiving the inhibitors plus amphotericin B. These experiments suggest that both transcription and translation are necessary for amphotericin B–induced IL-1β to appear in the supernatants of monocyte cultures.

Discussion

Amphotericin B results in a febrile response in humans, which peaks at ∼90 min after infusion and continues for up to 3 h. Chills and hypotension are also commonly observed [1]. These ADRs are reminiscent of those observed with administration of LPS, suggesting that amphotericin B causes the release of IL-1β or TNF-α protein, systemically. Therapy with amphotericin B is often hindered when these reactions occur. In clinical trials, only ibuprofen, hydrocortisone, and meperidine have proven effective for prophylaxis of these adverse effects [20]. Concomitant administration of nonsteroidal antiinflammatory agents with amphotericin B may not be prudent, as both produce detrimental effects on renal function [21]. Similarly, use of corticosteroids in patients with invasive fungal infections is controversial, especially in those with compromised immune function [22]. Insight into the mechanism of the infusion-related ADRs could suggest new or different pharmacologic interventions that would lessen undesired side effects and possibly broaden acceptability and use of this drug.

In vitro, amphotericin B stimulation of monocytes enhances phagocytic activity [23, 24], increases nitric oxide, and causes release of proinflammatory cytokines in culture supernatants, as described [4, 5, 25]. In human mononuclear leukocytes and
murine macrophages in vitro, amphotericin B induces the production of prostaglandin E₂, TNF-α, and IL-1β [3, 4, 25]. The mechanism of this cytokine induction has not been previously investigated, nor has the production of potential antiinflammatory mediators, such as sIL-1Ra, in response to amphotericin B. We questioned whether amphotericin B simply affects the cell (or its membrane) so as to result in release of preformed IL-1β into serum or culture supernatants or if it induces transcription and translation of the genes encoding for these proinflammatory cytokines analogous to LPS.

LPS has effects on monocytes and neutrophils similar to those just described for amphotericin B and is a known inducer of genes encoding inflammatory cytokines. It induces IL-1β and TNF-α transcription and releases a translational block on small amounts of TNF-α mRNA present in resting monocytes. If LPS is an accurate model for the mechanism of amphotericin B-induced cytokine expression, amphotericin B should induce detectable gene transcription and translation, and this should be necessary for the subsequent cytokine protein secretion. In the work presented here, we have demonstrated that amphotericin B induces not only transcription of IL-1β, TNF-α, and sIL-1Ra but also translation of IL-1β mRNA.

Using Northern and slot blot analysis, we show that monocytes increased levels of IL-1β and TNF-α mRNA in response to amphotericin B stimulation. Although Northern and slot blot analysis readily identified mRNA production, poor resolution did not allow for an adequate time course study. RT-PCR resulted in clearer kinetics, which roughly agreed with findings obtained by Northern blot analysis. Using RT-PCR, we have demonstrated that amphotericin B–induced IL-1β mRNA was present at 0.5 h and that peak production occurred between 1 and 4 h. Messenger RNA is therefore present immediately before and during the window of 60–180 min after amphotericin B infusion, when ADRs are most frequently observed. This is consistent with our previously reported in vitro observations of IL-1β protein [3]. No significant IL-1α mRNA was found to be induced by amphotericin B in THP-1 cells.

Compared with LPS stimulation, amphotericin B stimulation resulted in delayed TNF-α mRNA production, with mRNA present at 1 h and peak production occurring at 2 h. Peak TNF-α protein expression occurred outside of the time period of 60–180 min after infusion in previous studies [4, 5]. It is known that monocytes may have preformed TNF-α mRNA in the resting state. However, we have not yet directly examined
whether amphotericin B induces significant translation of TNF-α mRNA that may be present in resting or fungal antigen–stimulated human monocytes.

Secreted IL-1Ra is a 22-kDa protein that is synthesized and secreted primarily by monocytes/macrophages and is thought to regulate the biologic effects of IL-1β in vivo [26]. LPS has been shown to induce gene expression of sIL-1Ra, with protein being detectable as early as 2–4 h. Although homologous to IL-1β, sIL-1Ra is not capable of triggering the response observed with IL-1β on binding to the signal-transducing type I IL-1 receptor. While both molecules bind to this receptor with almost equal affinity, a 10- to 100-fold molar excess of IL-1Ra is required to inhibit IL-1 activity [7]. We observed increased sIL-1Ra in THP-1 cells at 24 and 48 h after stimulation with amphotericin B. Messenger RNA production was also demonstrated by RT-PCR and was higher at 24 h than at 6 h. Protein production continued after 24 h of amphotericin B stimulation. In this report, sIL-1Ra was induced by amphotericin B to >5 mg/mL at 24 h, which is >10-fold over the observed levels of IL-1β, suggesting possible involvement of sIL-1Ra in the attenuation of the often self-limited amphotericin B infusion–related ADRs.

Cycloheximide interrupts peptidyl transferase, preventing elongation of the amino acid chain in protein synthesis [27]. This agent successfully blocked translation of amphotericin B–induced IL-1β in a dose-dependent manner. Actinomycin D is an inhibitor of transcription that binds to genomic DNA, forming a stable complex that prevents the action of DNA polymerase [27]. It was effective in blocking amphotericin B–induced transcription of the IL-1β gene. Inhibition of IL-1β protein production by these agents demonstrates that both transcription and translation are necessary for amphotericin B–induced expression of IL-1β in human mononuclear cells. The observation that amphotericin B–induced IL-1β was suppressed nearly to baseline with actinomycin D and cycloheximide would suggest that amphotericin B does not increase secretion of preformed protein, or translation of preformed message, but activates expression of the IL-1β gene in human mononuclear cells.

We previously demonstrated that patients with severe amphotericin B reactions had a measurable increase in serum IL-1β compared with that in matched control patients [13]. Arning et al. [14] attempted to correlate serum expression of TNF-α, IL-6, and IL-1Ra levels with infusion-related reactions in patients receiving three different formulations of amphotericin B. These investigators were unable to associate TNF-α or IL-1Ra with infusion-related reactions in these patients, although increased IL-6 concentrations were observed in some patients experiencing these reactions. In those studies, IL-1β concentrations were not measured. The data presented here confirm our previous results suggesting that IL-1β is the initial inflammatory cytokine induced by amphotericin B, with TNF-α responding secondarily. Therefore, IL-1β appears to be the primary cytokine involved in the amphotericin B infusion reaction.

Our results are somewhat consistent with the work of Arning et al. [14], who found IL-1Ra to be expressed between 1 and 4 h after exposure to amphotericin B in some but not all patients, although this did not correlate with development of the ADRs. A direct effect of fungal antigens on monocytes or neutrophils cannot be excluded as the source of high levels of IL-1Ra in vivo, which were unchanged with amphotericin B administration in some patients. IL-1Ra may be responsible for the resolution and subsequent attenuation of amphotericin B infusion reactions. Increased constitutive expression of IL-1Ra may explain in part the heterogeneity observed in the frequency of these reactions among the population. Further investigation into the role of IL-1Ra and other antiinflammatory cytokines such as IL-4 and IL-10, as well as soluble IL-1 receptors, may be warranted. Such studies could lead to a role for IL-1Ra therapy in treatment of amphotericin B reactions, especially in view of the fact that no alterations in immune function occur with its administration.

In summary, we have observed through Northern and slot blot analysis and RT-PCR that amphotericin B increases transcription of IL-1β, TNF-α, and sIL-1Ra in THP-1 cells. Amphotericin B–induced IL-1β expression was inhibited by cycloheximide and actinomycin D in a dose-dependent manner. We conclude that amphotericin B induces gene expression in human monocyteic cells. Our data and previous reports suggest that IL-1β is the primary cytokine involved in amphotericin B infusion–related ADRs and suggests that these ADRs are moderated in part by IL-1Ra. Further investigation is needed to elucidate the cellular and nuclear mechanisms involved in amphotericin B–induced cytokine expression. Additional study of the relationship between amphotericin B and these cytokines may point to a role for IL-1Ra as a premedication for amphotericin B infusion–related ADRs. An understanding of the mechanism by which amphotericin B specifically induces certain genes could lead to the development of specific therapy to prevent amphotericin B–related ADRs.

References


