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Donna O. McCarthy

Marquette University, donnalee.mccarthy@marquette.edu

Susan Murray

University of Wisconsin - Madison

Dawn Galagan

University of Wisconsin - Madison

James E. Gern

University of Wisconsin - Madison

Paul R. Hutson

University of Wisconsin - Madison

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Meperidine Attenuates the Secretion but Not the Transcription of Interleukin 1 β in Human Mononuclear Leukocytes

Donna O. McCarthy

School of Nursing, University of Wisconsin, Madison, WI

Susan Murray

School of Nursing, University of Wisconsin, Madison, WI

Dawn Galagan

Department of Pediatrics, School of Medicine, University of Wisconsin, Madison, WI

James E. Gern

Department of Pediatrics, School of Medicine., University of Wisconsin, Madison, WI

Paul R. Hutson

School of Pharmacy, and Department of Pediatrics, Medical School, University of Wisconsin, Madison, WI

Abstract

Background:

The infusion of amphotericin-B (AmB) often produces clinically distressing rigors and chills, which promptly abate with intravenous injection of meperidine, although its mechanism of action is unknown.

Objective:

To examine the effects of meperidine on the transcription or secretion of Interleukin 1 β (IL-1 β) in human mononuclear leukocytes (MNL) exposed in vitro to the lipopolysaccharide (LPS) contained in *Escherichia coli* endotoxin or to AmB.

Methods:

Blood was drawn from eight healthy adult volunteers. The blood was centrifuged, and the layer containing MNL was separated; incubated with various combinations of medium, meperidine, and AmB; then tested for IL-1 content to determine the effect of meperidine on MNL secretion of IL-1 β . To determine the effect on MNL transcription of IL-1 β , the RNA was extracted from cells and the IL-1 β was measured using one of two different methods.

Results:

Incubation of human MNL in the presence of LPS or AmB significantly increased transcription of IL-1 β mRNA and secretion of IL-1 β . Addition of meperidine to these cultures significantly reduced LPS-induced, but not AmB-induced, secretion of IL-1 β *in vitro*. Meperidine did not alter IL-1 β mRNA levels in MNL exposed to LPS or AmB.

Conclusions:

These data suggest that meperidine decreases rigors and chills in part by decreasing MNL secretion of IL-1 β through a posttranscriptional mechanism.

Keywords:

amphotericin-B, meperidine, interleukin-1, endotoxin, mononuclear leukocytes

Fever is a stereotypical response to infection and injury that is mediated by small immunoregulatory peptides such as interleukin 1 alpha (IL-1 α), interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), tumor necrosis factor (TNF), or interferons that are secreted by activated leukocytes (Kluger, 1991; Mackowiak, 1992). These peptides stimulate prostaglandin synthesis in the preoptic area of the anterior hypothalamus, which is believed to raise the set point for thermoregulation. With elevation of the thermoregulatory set point, the hypothalamus signals other areas of the brain to initiate mechanisms such as shivering and vasoconstriction to raise body heat content to match the higher set point, which may be accompanied by an increase in body temperature.

Laboratory studies of the biology of fever often use small doses of lipopolysaccharide (LPS), an *Escherichia coli* endotoxin, to induce fever without causing severe morbidity in the subjects. In vitro studies have shown that exposure of rat, human, or murine mononuclear leukocytes (MNL) to LPS induces the synthesis and release of IL-1 β , TNF, IL-6, and interferons. Each of these peptides in turn will induce fever when injected into humans or laboratory animals (Kluger, 1991; Mackowiak, 1992). With the development of specific antibodies to these peptides, it has been shown that IL-1 β , IL-6, and TNF do not act independently as endogenous pyrogens, but rather in a complex network of overlapping as well as inhibitory interactions (Kluger; Mackowiak). These interactions affect both the duration and magnitude of the febrile response (Kluger, 1991; Long, Otterness, Kunkel, Vander, & Kluger, 1990; Rothwell et al., 1991).

Amphotericin-B (AmB) is an antifungal agent used in the management of systemic fungal infections. Shaking chills and fever occur in over half the patients infused with AmB (Gallis, Drew, & Pickard, 1990). In vitro studies have shown that exposure of murine or human MNL to AmB stimulates synthesis of TNF (Chia & Pollack, 1989; Tokuda et al., 1993) and IL-1 β (Cleary, Chapman, & Nolan, 1992; Gelfand, Kimball, Burke, & Dinarello, 1988; Matsumoto et al., 1993). Then synthesis of these pyrogenic peptides by MNL exposed to AmB may explain in part the onset of rigors and chills in patients infused with this drug.

Opioids and opioid receptors are also involved in thermoregulation (Spencer, Hruby, & Burks, 1990) and the neurobiology of fever (Blatteis, Xin, & Quan, 1991; Nakashima et al., 1995; Romanovsky, Shido, Ungar, & Blatteis, 1994). In this regard, meperidine, a synthetic opioid receptor agonist, is clinically effective in reducing rigors and chills in patients infused with AmB (Burks, Aisner, Fortner, & Wiernik, 1980; Gallis et al., 1990) or with stored blood products (Winqvist, 1991), which may contain TNF, IL-1, and IL-6 (Muylle, Joos, Wouters, De Bock, & Peetermans, 1993).

It was recently reported that injection of meperidine would block the onset of fever in laboratory rats injected with LPS and partially attenuate the fever induced by injection of IL-1 α (McCarthy, Daun, & Hutson, 1993). Exposure of human MNL to opioid agonists significantly reduced LPS-induced secretion of IL-1 β (Brummitt, Sharp, Gekker, Keane, & Peterson, 1988; McCarthy et al., 1993) and TNF (Chao, Molitor, Close, Hu, & Peterson, 1993) from human MNL in vitro. Thus, meperidine may attenuate rigors and chills by lowering circulating levels of endogenous pyrogens. Alternatively, it is possible that meperidine attenuates rigors and chills by lowering the febrile set point through IL-1 β or opioid receptors in areas of the brain involved in fever production or thermoregulation.

The present laboratory study was undertaken to determine whether meperidine alters the transcription or secretion of IL-1 from human MNL exposed in vitro to LPS or AmB. Laboratory models of MNL secretion of immunoregulatory pyrogenic peptides can be used to increase our understanding of the febrile response to infection and injury. Such knowledge is prerequisite to the scientific basis of nursing interventions to monitor and manage febrile episodes in acutely ill patients.

Methods

Effect of Meperidine on MNL Secretion of IL-1 β : Between 20 and 50 ml of blood were drawn into a heparinized syringe from a vein in the antecubital fossa of eight healthy adult volunteers. The blood was aseptically diluted 1:1 in phosphate buffered saline (PBS) and separated by density centrifugation as described by McCarthy et al. (1993). The layer containing MNL was washed twice in PBS, counted using trypan blue, and resuspended at 2×10^6 viable cells per 1 ml of RPMI 1640 supplemented with 2 mM glutamine, 10 mM HEPES, 10% fetal calf serum, 100 units/ml penicillin, and 100 mg/ml streptomycin (medium). One ml aliquots of cells were incubated for 18 hours overnight at 37°C in a humidified atmosphere of 5% CO₂ in medium alone or medium containing 10 μ g LPS, 10 μ g LPS and 10 μ g meperidine, 2 μ g AmB, or 2 μ g AmB and 10 μ g meperidine. The cell-free culture fluids were collected by centrifugation and frozen at -4°C. All solutions and reagents were obtained from Sigma Chemical Company (St. Louis, MO).

The IL-1 content of the culture fluids was determined using an enzyme-linked immunosorbent assay for human IL-1 β (R&D Systems, Minneapolis, MN) per manufacturer's instructions. Data are reported as mean ng/ml \pm SE of IL-1 β based on a standard dilution of rhIL-1 β read at 490 nm using a microtitre spectrophotometer (Biotech Instruments, Winooski, VT). Because of the large between-subject variance, data were analyzed using the nonparametric rank-sum test.

Effect of Meperidine of MNL Transcription of IL-1 β : One ml aliquots of 2×10^6 viable cells were incubated for 2 hours in medium alone, medium plus 10 μ g LPS, 10 μ g LPS and 10 μ g meperidine, 2 μ g/ml AmB, or 2 μ g AmB and

10 µg meperidine. At the end of 2 hours, the cells were centrifuged and the supernatant removed. Pilot studies had indicated the greatest increase in IL-1 β mRNA of cells stimulated with 10 µg/ml LPS was at 2 hours versus 1 or 4 hours after stimulation. Total RNA was extracted from the cell pellets and IL-1 β mRNA was measured using one of two different methods. For both methods, a twofold change in IL-1 β mRNA content was regarded as biologically significant.

In the first method, cytoplasmic extracts containing RNA from 4 donors were prepared by lysing cells in 50 µl 10 mM Tris-HCl/1mM EDTA (edetic acid) with 0.5% Nonidet P 40 (Sigma Chemical Co., St. Louis, MO) for 10 minutes on ice (Coutlee et al., 1990). The cytoplasmic RNA was then hybridized in solution with 25 ng biotin-labeled IL-1 β cDNA probe. Fifty µl of the hybridization mixture was added to quadruplicate wells of a black 96-well microtiter plate (Microfluor; Dynatech Labs, Chantilly, VA) that was precoated with 50 µ per well of 2 µg/ml mouse anti-biotin monoclonal antibody (Zymed, South San Francisco, CA). The plates were incubated for 2 hours, washed, and incubated again for 2 hours with 50 µl of a 0.025% solution containing the Fab fragments of a monoclonal antibody to DNA-RNA hybrids conjugated to alkaline phosphatase (Gern et al., 1996). After washing, substrate (4-methylumbelliferyl phosphate; Sigma Chemical Co., St. Louis, MO) was added, and the plates were incubated for 24 hours. Fluorescence (excitation wavelength, 360 nm; emission wavelength, 460 nm) was measured in a microtiter plate fluorometer (model 7600; Cambridge Technology, Watertown, MA). The coefficient of variation of this assay was 8.3%. A stimulation index was computed by dividing each of the culture conditions by the fluorescence units of IL-1 mRNA detected in cells incubated in medium alone.

Because it is difficult to ensure that cell pellets contain equal amounts of total RNA in the beginning, the expression of IL-1 β mRNA in the cells of the remaining four donors was assessed using Southern blotting of polymerase chain reaction (PCR) products. Southern blotting of PCR products allows comparison of expression of the gene of interest, IL-1 β , to one that should not vary, such as G3PDH. Thus, the amount of IL-1 β mRNA in any given test sample is normalized to the amount of G3PDH mRNA in the same sample.

For this method, total RNA in the cell pellets of 4 donors was isolated using a phenol/chloroform extraction reagent (Tri Reagent; Sigma, St. Louis, MO) according to manufacturer's instruction. After resuspending the RNA in 50 µl of double distilled water, 8 µl of RNA solution was incubated at 37°C for 1 hour with 200 U reverse transcriptase (Gibco, Grand Island, NY), 5 µl of 10 \times reaction buffer, 0.01 mM DTT 40 U RNasin, 0.5 µg of random primers, and 0.5 mM dNTPs (Promega, Madison, WI). For PCR, the cDNA solution was diluted 1:5 and 4 µl were incubated (24 cycles of denaturation at 94°C for 45 seconds, annealing at 60°C for 45 seconds, and extension at 72°C for 2 minutes) with 2 U Taq DNA polymerase (Promega, Madison, WI) and 1 µl each of upstream (5' ATG GCA GAA GTA CCT AAG CTC GC) and downstream (5' ACAC AAA TTG CAT GGT GAA GTC AGT T) IL-1 β primers (Clontech, Palo Alto, CA). A 4-µl aliquot from the same cDNA product was also incubated with 1 µl each of G3PDH primers (upstream 5' TGA AGG TCG GAG TCA ACG GAT TTG GT; downstream 5' CAT GTG GGC CAT GAG GTC CAC CAC) (Clontech, Palo Alto, CA).

The number of PCR cycles was adjusted for each set of primers to maintain a linear relationship between mRNA and the PCR products so that quantitative comparisons of PCR products could be obtained. In addition, a reference standard curve consisting of fourfold dilutions of cDNA from a highly positive sample was included in each PCR run. The PCR products were visualized by agarose electrophoresis, and their identity was confirmed by Southern blotting onto a neutral nylon membrane using a commercial kit (ECL System; Amersham, Arlington Heights, IL) and biotin-labeled cDNA probes specific for IL-1 β and G3PDH (Clontech, Palo Alto, CA). These probes were synthesized using PCR, using the same primers described previously and plasma-purified IL-1 or G3PDH cDNA as a template. The blot image was scanned and converted into a digital file and was then analyzed by densitometry (SigmaStat; Jandel Scientific, San Rafael, CA) to quantitate mRNA levels for IL-1 β and G3PDH cDNA in comparison with the standard curves described previously. The IL-1 β mRNA levels were normalized by subtracting out the amount of G3PDH mRNA in the same sample.

Results

Effect of Meperidine on MNL Secretion of IL-1 β : As shown in [Figure 1](#), the culture fluids of human peripheral blood MNL incubated overnight in medium alone contained $.02 \pm .01$ ng/ml IL-1 β (range .002 to .13 ng/ml). Culture fluids of MNL incubated in medium with meperidine contained $.03 \pm .02$ ng/ml of IL-1 β (range.002 to .16 ng/ml). The IL-1 β content of culture fluids from MNL incubated in medium with LPS was 15.1 ± 2.6 ng/ml (range 3.4 to 24.9 ng/ml), which was significantly greater than fluids from cells incubated in medium alone ($Z = -2.5, p = .01$). Addition of meperidine to the cultures of MNL incubated in medium with LPS significantly reduced the amount of IL-1 β to 8.5 ± 3.0 ng/ml (1.7 to 26.6 ng/ml; $Z = -2.1, p = .03$).

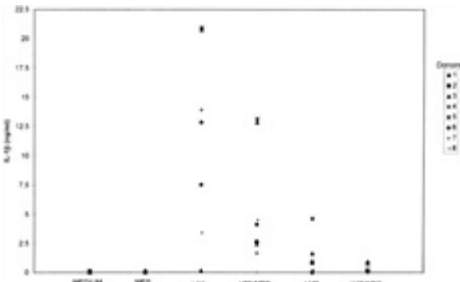


FIGURE 1: Levels of IL-1 β (ng/ml) in culture fluids of mononuclear leukocytes from 8 donors incubated in medium alone or medium plus meperidine (MEP), E. coli endotoxin (LPS), LPS and meperidine(LPS/MEP), Amphotericin-B (AMB), or AmB and meperidine (AMB/MEP).

The IL-1 β content of culture fluids from MNL incubated in medium with AmB was 1.1 ± 5 ng/ml (0 to 4.6 ng/ml), which was significantly greater than fluids from cells incubated in medium alone ($Z = -2.1, p = .03$). In contrast, the IL-1 β content of culture fluids from MNL incubated in medium with AmB plus meperidine was $.4 \pm 2$ ng/ml (0 to 1.4 ng/ml) and was not significantly different from that of cells exposed to AmB alone ($Z = -1.3, p = .2$).

Effect of Meperidine on MNL Transcription of IL-1 β : As shown in [Table 1](#), incubation of MNL in medium containing 10 μ g/ml meperidine produced a twofold increase in IL-1 β mRNA levels compared with cells incubated in medium alone, when measured by fluorescent enzyme-linked immunosorbent assay (ELISA) (range 0.5 to 3.3) or by Southern blotting of the RT-PCR product (range 0.9 to 3.9). Exposure of cells to 10 μ g/ml LPS increased the IL-1 β mRNA levels by fourfold(range 2.5 to 6.5) or by sixfold (range 2 to 11.8), respectively. The level of IL-1 β mRNA of cells exposed to LPS with 10 μ g/ml meperidine were increased threefold (2.1 to 4.2) above medium alone when measured by fluorescent ELISA, or 10-fold (2.2 to 16.0) when measured by Southern blotting. Thus, the addition of meperidine did not retard the transcription of IL-1 β mRNA in cells exposed to LPS.

TABLE 1: Stimulation Index^a for IL-1 β mRNA Levels

	MEP	LPS	LPS/MEP	AMB	AMB/MEP
Florescent ELISA donor					
1	3.3	6.5	3.7	9.0	7.0
2	2.0	3.1	2.6	3.4	2.3
3	0.5	2.5	2.1	2.3	2.1
4	2.6	4.9	4.2	7.4	4.9
Southern Blots of RT-PCR donor					
5	3.9	9.2	12.8	3.1	2.6
6	0.9	11.8	9.2	8.7	7.5
7	1.1	2.0	2.2	1.5	1.5
8	1.0	4.0	16.0	9.8	10.0

^aCompared with levels in cells incubated in medium alone.

Note: Refer to Figure 1 for definition of terms.

The IL-1 β mRNA levels in cells exposed to AmB were increased 5.5-fold (2.3 to 9.0) above that of cells incubated in medium alone when measured by fluorescent ELISA, or 5.8-fold (1.5 to 9.8) when measured by Southern blotting, respectively. The IL-1 β mRNA content of cells exposed to AmB and meperidine was fourfold greater than cells exposed to medium alone (range 2.1 to 7.0) when measured by ELISA, or fivefold above medium (range 1.5 to 10.0) when measured by Southern blotting of rt-PCR products. In neither case did the addition of meperidine reduce the transcription of IL-1 mRNA in cells exposed to AmB.

Discussion

The onset of fever after infection or injury is believed to be mediated by MNL synthesis and release of pyrogenic peptides such as IL-1 β (Kluger, 1991). The onset of fever is frequently accompanied by shivering, which is believed to increase body heat content (Holtzclaw, 1990). Shivering and chills are also seen in patients infused with blood products or amphotericin- β . Meperidine is frequently used in these clinical settings to abate rigors and chills, although its mechanism of action is not known.

In the present study, in vitro exposure of human MNL to LPS was found to significantly increase IL-1 β mRNA and IL-1 β secretion above that of cells incubated in the presence of medium alone. Addition of meperidine to cultures of human MNL stimulated with LPS significantly reduced the amount of IL-1 β detected in the culture fluids of the cells but did not effectively reduce IL-1 β mRNA levels. These data suggest that the antipyretic effect of meperidine may be caused by, at least in part, decreased MNL secretion of IL-1 β after exposure to LPS.

These data are partially supported by Brummitt et al. (1988), who found that beta-endorphin suppressed the release of IL-1 β from stimulated human MNL, and by McCarthy et al. (1993), who found that meperidine did the same. Bian, Wang, and Li (1995) found that morphine decreased the secretion of IL-1 and TNF-like activity from stimulated murine MNL, and Karagouni and Hadjipetrou-Kourounakis (1990) reported that secretion of IL-1-like activity from LPS-stimulated murine adherent spleen cells was suppressed when the cells were exposed to either of two opioid agonists, morpholine or pethidine (meperidine).

In contrast, Apte, Durum, and Oppenheim (1990) reported that beta-endorphin significantly increased IL-1-like activity in culture fluids of LPS-stimulated murine bone marrow macrophages. These authors suggest that the net effect of an opioid agonist or antagonist on IL-1 release might be a function of the multiple subtypes of opioid receptors present on leukocytes (Apte et al., 1990). These receptors have considerable patterns of cross-reactivity (Carr, 1991), and their density appears to increase with maturation or activation of the cell (Carr; Roy, Ge, Ramakrishnan, Lee, & Loh, 1991).

Exposure of human MNL in vitro to AmB has been shown to induce the secretion of IL-1 β (Cleary et al., 1992; Gelfand et al., 1988). It is tempting to speculate that meperidine attenuates fever and chills in patients infused with AmB by reducing MNL secretion of IL-1 β . In the present study, in vitro exposure of human MNL to AmB significantly increased IL-1 β mRNA levels and secretion of IL-1 β compared with cells incubated in medium alone. Addition of meperidine to these cultures did not alter IL-1 β mRNA levels or IL-1 β secretion. These data are supported by those of Cleary et al., who reported that the addition of 1 to 10 μ g/ml of meperidine had no effect on AmB-induced release of IL-1 β from human MNL.

It is interesting to note that there was more than a log difference in the amount of IL-1 β secreted by MNL exposed to 10 μ g/ml LPS (15.1 ng/ml) as opposed to 2 μ g/ml AmB (1.1 ng/ml), and this was true for cells from seven of the eight donors. Cleary et al. (1992) found IL-1 β levels secreted by human MNL exposed to 0.1 μ g/ml of LPS to be greater than that of cells exposed to 10 μ g/ml AmB. These data suggest that AmB is not as potent a

stimulant of IL-1 β secretion as LPS. Additionally, in the present study there was great inter-subject variation in the release of IL-1 β from MNL stimulated with AmB (0 to 4.6 ng/ml), with cells from two donors secreting no detectable IL-1 β . The latter may explain in part why some patients experience rigor and chills during infusion of amphotericin and others do not.

The results of the present study do not rule out the possibility that the antipyretic effects of meperidine are mediated centrally via opioid receptors involved in thermoregulation (Spencer, Hruby, & Burks, 1990) or neuromodulation of fever (Blatteis et al., 1991; Nakashima et al., 1995; Romanovsky et al., 1994). Peripheral injection of LPS is associated with increased beta-endorphin in the cerebrospinal fluid of rats (Murphy, Koenig, & Lipton, 1983) and increased expression of IL-1 α and IL-1 β mRNA in the brains of mice (Ban, Haour, & Lenstra, 1992). Wiedermann (1989) demonstrated that preincubation of fresh-frozen rat brain slices with rhIL-1 enhanced the specific binding of radiolabeled beta-endorphin to opioid receptors in a dose-dependent fashion, including areas of the brain involved in the neuromodulation of fever. Clearly, further study of the clinical effects of opioid receptor agonists on regulation of body temperature in febrile versus nonfebrile patients is needed.

Research has shown that as set point for regulation of body temperature is raised, so too is the temperature threshold at which thermogenesis is initiated to defend the higher body temperature (Banet, 1988). The lowering of the set point for thermoregulation may explain, at least in part, the mechanism by which meperidine attenuates shaking chills in febrile patients subjected to physical cooling methods, such as hypothermia blankets (Banet, 1988; Caruso, Hadley, Shukla, Frame, & Houry, 1992; Holtzclaw, 1990). The potential additive or synergistic effects of meperidine with antipyretic nonsteroidal drugs, such as acetaminophen or ibuprofen, or with physical cooling methods, warrants further study lest febrile patients be subjected to untoward levels of antipyresis.

References

- Apte, R. N., Durum, S. K., & Oppenheim, J. J. (1990). Opioids modulate interleukin-1 production and secretion by bone-marrow macrophages. *Immunology Letters*, 24, 141-148.
- Ban, E., Haour, F., & Lenstra, R. (1992). Brain interleukin-1 gene expression induced by peripheral lipopolysaccharide administration. *Cytokine*, 4, 48-54.
- Banet, M. (1988). Mechanism of action of physical antipyresis in the rat. *Journal of Applied Physiology*, 64, 1076-1078.
- Bian, T. H., Wang, X. F., & Li, X. Y. (1995). Effect of morphine on interleukin-1 and tumor necrosis factor alpha production from mouse peritoneal macrophages in vitro. *Acta Pharmacologica Sinica*, 16, 449-451.
- Blatteis, C. M., Xin, L., & Quan, N. (1991). Neuromodulation of fever: Apparent involvement of opioids. *Brain Research Bulletin*, 26, 219-223.
- Brummitt, C. F., Sharp, B., Gekker, G., Keane, W. F., & Peterson, P. K. (1988). B-endorphin inhibits interleukin 1b release by human peripheral blood mononuclear cells. In M. C. Powanda, J. J. Oppenheim, M. J. Kluger, & C. A. Dinarello (Eds.), *Monokines and other non-lymphocytic cytokines* (pp. 125-130). New York: Liss.
- Burks, L. C., Aisner, J., Fortner, C. L., & Wiernik, P. H. (1980). Meperidine for the treatment of shaking chills and fever. *Archives of Internal Medicine*, 140, 483-484.
- Carr, D. J. (1991). The role of endogenous opioids and their receptors in the immune system. *Proceedings of the Society for Experimental Biology & Medicine*, 198, 710-720.
- Caruso, C. C., Hadley, B. J., Shukla, R., Frame, P., & Houry, J. (1992). Cooling effects and comfort of four cooling blanket temperatures in humans with fever. *Nursing Research*, 41, 68-72.
- Chao, C. C., Molitor, T. W., Close, K., Hu, S., & Peterson, P. K. (1993). Morphine inhibits the release of tumor necrosis factor in human peripheral blood mononuclear cell cultures. *International Journal of Immunopharmacology*, 15, 447-453.

- Chia, J. K., & Pollack, M. (1989). Amphotericin B induces tumor necrosis factor production by murine macrophages. *Journal of Infectious Diseases*, 159, 113-116.
- Cleary, J. D., Chapman, S. W., & Nolan, R. L. (1992). Pharmacologic modulation of interleukin-1 expression by amphotericin B-stimulated human mononuclear cells. *Antimicrobial Agents and Chemotherapy*, 36, 977-981.
- Coutlee, F., Rubalcaba, E. A., Viscidi, R. P., Gern, J. E., Murphy, P. A., & Lederman, H. M. (1990). Quantitative detection of messenger RNA by solution hybridization and enzyme immunoassay. *Journal of Biological Chemistry*, 265, 11601-11604.
- Gallis, H. A., Drew, R. H., & Pickard, W. W. (1990). Amphotericin B: 30 years of clinical experience. *Review of Infectious Diseases*, 12, 308-329.
- Gelfand, J. A., Kimball, K., Burke, J. F., & Dinarello, C. A. (1988). Amphotericin B treatment of human mononuclear cells in vitro results in secretion of tumor necrosis factor and interleukin-1. *Clinical Research*, 36, 456A.
- Gern, J. E., Dick, E. C., Lee, W. M., Murray, S., Meyer, K., Handzel, Z. T., & Busse, W. W. (1996). Rhinovirus enters but does not replicate inside monocytes and airway macrophages. *Journal of Immunology*, 156, 621-627.
- Holtzclaw, B. J. (1990). Control of febrile shivering during amphotericin B therapy. *Oncology Nursing Forum*, 17, 521-524.
- Karagouni, E. E., & Hadjipetrou-Kourounakis, L. (1990). Interleukins counteract opioid agonists immunosuppression. *International Journal of Neuroscience*, 54, 157-163.
- Kluger, M. J. (1991). Fever: Role of pyrogens and cryogens. *Physiology Reviews*, 71, 93-127.
- Long, N. C., Otterness, I., Kunkel, S. L., Vander, A. J., & Kluger, M. J. (1990). Roles of interleukin 1b and tumor necrosis factor in lipopolysaccharide fever in rats. *American Journal of Physiology*, 259, R724-R728.
- Mackowiak, P. A. (1992). Mechanisms of fever. *Current Opinion in Infectious Diseases*, 5, 348-354.
- Matsumoto, T., Kaku, M., Furuya, N., Usui, T., Kohno, S., Tomono, K., Tateda, K., Hirakata, Y., & Yamaguchi, K. (1993). Amphotericin B-induced resistance to *Pseudomonas aeruginosa* infection in mice. *Journal of Antibiotics*, 46, 777-784.
- McCarthy, D. O., Daun, J. M., & Hutson, P. R. (1993). Meperidine attenuates the febrile response to endotoxin and interleukin-1 alpha in rats. *Nursing Research*, 42, 363-367.
- Murphy, M. T., Koenig, J. I., & Lipton, J. M. (1983). Changes in central concentration of b-endorphin in fever. *Federation Proceedings*, 42, 464.
- Muyllé, L., Joos, M., Wouters, E., De Bock, R., & Peetermans, M. E. (1993). Increased tumor necrosis factor alpha (TNF alpha), interleukin 1, and interleukin 6 (IL-6) levels in the plasma of stored platelet concentrates: Relationship between TNF alpha and IL-6 levels and febrile transfusion reactions. *Transfusion*, 33, 195-199.
- Nakashima, T., Murakami, T., Murai, Y., Hori, T., Miyata, S., & Kiyohara, T. (1995). Naloxone suppresses the rising phase of fever induced by interferon-alpha. *Brain Research Bulletin*, 37, 61-66.
- Romanovsky, A. A., Shido, O., Ungar, A. L., & Blatteis, C. M. (1994). Peripheral naloxone attenuates lipopolysaccharide fever in guinea pigs by an action outside the blood-brain barrier. *American Journal of Physiology*, 266, R1824-R1831.
- Rothwell, N. J., Busbridge, N. J., Lefeuve, R. A., Hardwick, A. J., Gauldie, J., & Hopkins, S. J. (1991). Interleukin-6 is a centrally acting endogenous pyrogen in the rat. *Canadian Journal of Physiology & Pharmacology*, 69, 1465-1469.
- Roy, S., Ge, B.-L., Ramakrishnan, S., Lee, N. M., & Loh, H. H. (1991). [3-H] morphine binding is enhanced by IL-1 stimulated thymocyte proliferation. *Federation of European Biochemical Societies*, 287, 93-96.
- Spencer, R. L., Hruby, V. J., & Burks, T. F. (1990). Alteration of thermoregulatory set point with opioid agonists. *Journal of Pharmacology and Experimental Therapeutics*, 252, 696-705.

- Tokuda, Y., Tsuji, M., Yamazaki, M., Kimura, S., Abe, S., & Yamaguchi, H. (1993). Augmentation of murine tumor necrosis factor production by amphotericin B in vitro and in vivo. *Antimicrobial Agents and Chemotherapy*, 37, 2228-2230.
- Wiedermann, C. J. (1989). Interleukin-1 interaction with neuroregulatory systems: Selective enhancement by recombinant human and mouse interleukin-1 of in vitro opioid peptide receptor binding in rat brain. *Journal of Neuroscience Research*, 22, 172-180.
- Winqvist, I. (1991). Meperidine (pethidine) to control shaking chills and fever associated with non-hemolytic transfusion reactions. *European Journal of Haematology*, 47, 154-155.