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Epinephrine inhibits endotoxin-induced IL-1β production: roles of tumor necrosis factor-α and IL-10

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Van der Poll, Tom, and Stephen F. Lowry. Epinephrine inhibits endotoxin-induced IL-1β production: roles of tumor necrosis factor-α and IL-10. *Am. J. Physiol.* 273 (*Regulatory Integrative Comp. Physiol.* 42): R1885–R1890, 1997.— Epinephrine has been found to inhibit the production of the proinflammatory cytokine tumor necrosis factor (TNF)-α and to enhance the production of anti-inflammatory cytokine interleukin (IL)-10. To determine the effect of epinephrine on IL-1β production, the following experiments were performed: *1*) blood obtained from subjects at 4–21 h after the start of a continuous infusion of epinephrine (30 $ng \cdot kg^{-1} \cdot min^{-1}$) produced less IL-1β after ex vivo stimulation with lipopolysaccharide (LPS), compared with blood drawn from subjects infused with saline; *2*) in whole blood in vitro, epinephrine caused a dose-dependent decrease in LPS-induced IL-1β production, which was likely mediated via adrenergic receptors; and *3*) inhibition of TNF and enhancement of IL-10 both contributed to epinephrine-induced inhibition of IL-1β production. Epinephrine, either endogenously produced or administered as a component of sepsis treatment, may attenuate excessive activity of proinflammatory cytokines early in the course of systemic infection.

adenosine 3′,5′-cyclic monophosphate; lipopolysaccharide; cytokines; adrenergic receptors ; interleukin-1β; interleukin-10

INTERLEUKIN (IL)-1 is a multifunctional cytokine that can exert effects on nearly every cell type (6). IL-1 is the designation for two polypeptides (IL-1α and IL-1β), each encoded by a separate gene on chromosome 2. Although most IL-1α remains in the cytosol of cells, IL-1β is the predominant type of IL-1 that can be found in the extracellular environment during disease. IL-1 has been implicated as a significant mediator of septic shock. IL-1β can be detected in baboons infused with a lethal dose of live *Escherichia coli* and in a subset of patients with sepsis (2, 11, 13), and administration of IL-1 to baboons or humans reproduces the major features of sepsis (9, 20). Moreover, neutralization of endogenous IL-1 activity in animal models of lethal endotoxemia or bacteremia by infusion of recombinant IL-1 receptor antagonist has a strong protective effect (10, 21).

In recent years it has become clear that catecholamines can influence the production of cytokines. Epinephrine has been found to inhibit the production of the proinflammatory cytokine tumor necrosis factor (TNF)-α by mononuclear cells or whole blood stimulated with lipopolysaccharide (LPS) in vitro, while simultaneously enhancing the production of the anti-inflammatory cytokine IL-10 (25, 29, 30). Accordingly, infusion of epinephrine in healthy humans exposed to an intravenous dose of LPS is associated with reduced TNF and increased IL-10 plasma concentrations (30). Hence, epinephrine may have a net anti-inflammatory effect on the cytokine network.

Knowledge of the effect of epinephrine on IL-1 production is limited. Such knowledge may not only have implications for the understanding of endogenous catecholamine effects during acute systemic infection but also for the therapeutic use of these hormones in patients with septic shock. It is difficult to determine the effect of epinephrine on LPS-induced IL-1 synthesis in humans in vivo, because in the widely adopted model of human endotoxemia, IL-1 is not released to the circulation in significant quantities (30, 31). Therefore, in the present study we sought to study this epinephrine effect under conditions that mimic the human in vivo situation as closely as possible, i.e., the IL-1β production capacity of whole blood was determined ex vivo before and during a continuous infusion of epinephrine in healthy humans in vivo. In addition, because epinephrine-induced inhibition of TNF and enhancement of IL-10 production found earlier in this model may influence IL-1β production (5, 8, 11, 30), we examined the roles of these cytokines in the observed epinephrine effect.

MATERIALS AND METHODS

Study design and subjects. There were 18 male subjects, aged 28 ± 1 (SE) yr, admitted to the Adult Clinical Research Center of the New York Hospital-Cornell University Medical Center after documentation of good health by history, physical examination, and hematological and biochemical screening. The study was approved by the Institutional Review Board, and written informed consent was obtained from all subjects before enrollment in the study. Subjects were randomized to receive either a constant intravenous infusion of epinephrine (Parke-Davis, Morris Plains, NJ; 30 $ng \cdot kg^{-1} \cdot min^{-1}$; $n = 8$), starting at 9 AM or an equivalent volume of normal saline ($n = 10$). Venous blood samples for whole blood stimulation were obtained before the start of the infusion and at 4, 8, and 21 h thereafter. Blood was collected aseptically with a sterile collecting system consisting of a butterfly needle connected to a syringe (Becton Dickinson, Rutherford, NJ). Anticoagulation was obtained with sterile heparin (Elkins-Sinn, Cherry Hill, NJ; 10 U/ml blood final concentration).

Whole blood stimulation. Whole blood was stimulated for 24 h at 37°C with LPS (10 ng/ml final concentration; *E. coli* serotype 0127:B8; Sigma Chemical, St. Louis, MO) in sterile polypropylene tubes (Becton Dickinson) as described previously (30). After the incubation, plasma was prepared by centrifugation and stored at −70°C until assays were performed. IL-1β levels were expressed as nanogram per 10^9 monocytes, because monocyte counts changed during infu-

sion of epinephrine (30) and monocytes are the major source of IL-1β (3).

In separate in vitro experiments, whole blood was diluted 1:1 in sterile RPMI-1640 supplemented with L-glutamine (GIBCO BRL, Life Technologies, Grand Island, NY). In these experiments, whole blood was incubated with LPS (10 ng/ml) in the presence or absence of the following agents: epinephrine (Parke-Davis), phentolamine (Ciba-Geigy, Basel, Switzerland), propranolol (Ayerst, Philadelphia, PA), phenylephrine (American Regent Laboratories, Shirley, NY), isoproterenol (Sanofi Winthrop Pharmaceuticals, New York, NY), dibutyryladenosine 3′,5′-cyclic monophosphate (DBcAMP, Sigma Chemical), neutralizing monoclonal antibodies directed against human TNF (3C3; Medgenix, Fleurus, Belgium), or human IL-10 (IF9, Medgenix, Fleurus, Belgium), and anti-human-follicle-stimulating hormone monoclonal antibodies (MAb; isotype-matched control antibody). For these in vitro experiments, polypropylene tubes were prefilled with 0.75 ml RPMI containing the appropriate concentrations of LPS, (anti-)adrenergic agents, and/or antibodies, after which 0.75 ml heparinized blood was added. Tubes were then gently mixed and placed in the incubator. After the incubation, plasma was prepared by centrifugation and stored at −70°C until assays were performed.

Assay. IL-1β was measured by enzyme-linked immunosorbent assay as described previously (18, 30).

Statistical analysis. All values are given as means ± SE. Serial data were compared by analysis of variance (ANOVA). Paired samples were compared with the Wilcoxon test for matched samples. $P < 0.05$ was considered to represent a statistically significant difference.

RESULTS

LPS-induced IL-1β production by whole blood ex vivo during epinephrine infusion. During infusion of saline, plasma epinephrine concentrations and monocyte counts did not change and remained normal (30). In addition, LPS-induced IL-1β production by whole blood was similar at all time points evaluated, indicating that there was no circadian rythmn that influenced LPS responsiveness of whole blood (Fig. 1). In subjects receiving a constant infusion of epinephrine, plasma epinephrine concentrations reached a plateau of 1,037 ± 179 pg/ml, whereas monocyte counts modestly increased (30). Epinephrine significantly attenuated LPS-induced IL-1β production in whole blood ($P < 0.05$ vs. saline infusion). This effect was noted within 4 h after initiation of epinephrine infusion and persisted throughout the 21-h observation period (Fig. 1).

Epinephrine inhibits IL-1β production via effect on β-adrenergic receptor. Next, we studied the mechanisms by which epinephrine inhibits IL-1β production in whole blood in vitro. Incubation of whole blood with LPS (10 ng/ml) caused an increase in IL-1β concentrations, peaking after 16 h (data not shown). Therefore, in subsequent experiments we used this incubation period. Epinephrine caused a dose-dependent inhibition of IL-1β production by whole blood incubated with LPS (Fig. 2, *top*). Because epinephrine binds to both α- and β-adrenergic receptors, we next assessed which adrenergic receptor was involved in the effects of epinephrine on IL-1β production. For this purpose, we incubated whole blood with LPS (10 ng/ml) in the presence or absence of epinephrine (10^{-6} M), the α-adrenergic

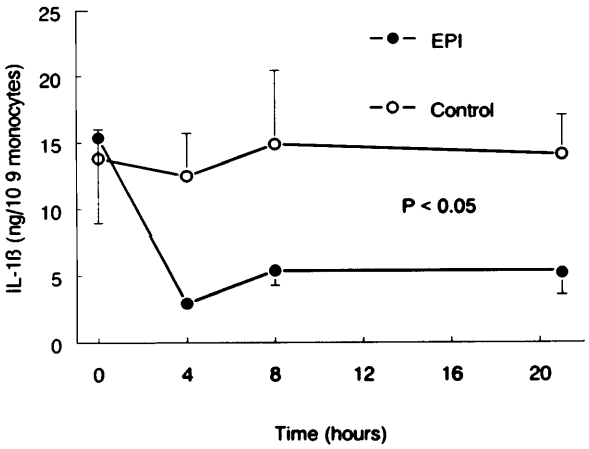

Fig. 1. Means ± SE plasma concentration of interleukin (IL)-1β (ng/10^9 monocytes) after stimulation of whole blood, obtained during constant intravenous infusion of epinephrine (Epi), with lipopolysaccharide (LPS). Blood was drawn directly before ($t = 0$) and during constant intravenous infusion of Epi (30 ng·kg^{-1}·min^{-1}, $n = 8$) or saline (control, $n = 10$) at $t = 4$, 8, and 21 h. Whole blood was then incubated with LPS (10 ng/ml) for 24 h at 37°C, after which plasma was collected. *P value indicates differences between Epi and control by analysis of variance.

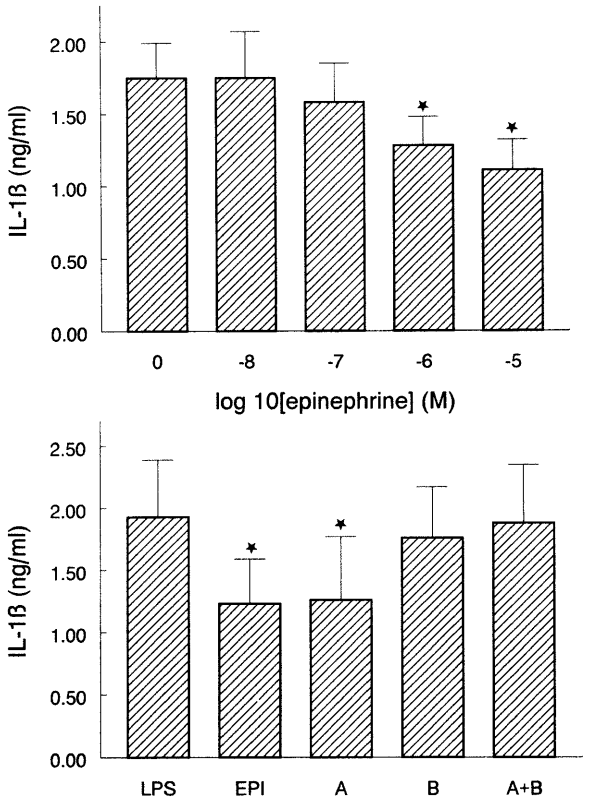

Fig. 2. Epi dose dependently inhibits LPS-induced IL-1β production via effect on β-adrenergic receptors. Whole blood diluted 1:1 in RPMI-1640 was incubated for 16 h with LPS (10 ng/ml) in presence or absence of increasing concentrations of Epi (*top*); *bottom*: effect of α- and/or β-receptor blockade. LPS, with LPS only; Epi, with Epi (10^{-6} M); A, with Epi (10^{-6} M) and α_1- and β_2-antagonist phentolamine (10^{-5} M); B, with Epi (10^{-6} M) and β_1- and β_2-antagonist propranolol (10^{-5} M); and A + B, with Epi, phentolamine, and propranolol. Data are means ± SE of 6 different donors. *$P < 0.05$ vs. LPS only.

receptor antagonist phentolamine (10^{-5} M), and/or the β-receptor antagonist propranolol (10^{-5} M). Blockade of α-receptors by phentolamine did not influence the epinephrine inhibition of IL-1β production. By contrast, propranolol completely prevented this effect (Fig. 2, *bottom*). To confirm that β-adrenergic receptor stimulation mediates the reduction of LPS-induced IL-1β production, we next incubated whole blood with LPS and specific α- or β-adrenergic agonists. As depicted in Fig. 3, isoproterenol (β-receptor agonist) was a potent inhibitor of LPS-induced IL-1β release. By contrast, phenylephrine (α-receptor agonist) did not influence IL-1β levels (Fig. 3).

DBcAMP inhibits IL-1β production. Because adrenergic stimulation is known to result in an elevation of intracellular adenosine 3′,5′-cyclic monophosphate (cAMP) levels (25, 32), we were interested to determine the effect of DBcAMP on IL-1β production. Addition of DBcAMP caused a dose-dependent decrease in IL-1β levels in LPS-stimulated whole blood (Fig. 4).

Inhibition of TNF production contributes to inhibition of IL-1β production by epinephrine. It has been demonstrated that the production of IL-1β during gram-negative bacteremia in vivo is partly dependent on TNF production (11). Inhibition of TNF production by epinephrine (30) could therefore contribute to epinephrine-induced inhibition of IL-1β production. To evaluate this possibility, we incubated whole blood with LPS (10 ng/ml) in the presence or absence of epinephrine (10^{-6} M), a neutralizing anti-TNF MAb (25 μg/ml), or an equivalent amount of an irrelevant isotype-matched control MAb (Table 1). Anti-TNF inhibited LPS-induced IL-1β production, indicating that TNF is partially responsible for LPS-induced IL-1β production in whole blood. Furthermore, in the presence of anti-TNF, epinephrine did not influence the production of IL-1β anymore. These data suggested that the inhibiting effect of epinephrine on IL-1β production is dependent on the concurrent inhibiting effect of epinephrine on TNF production.

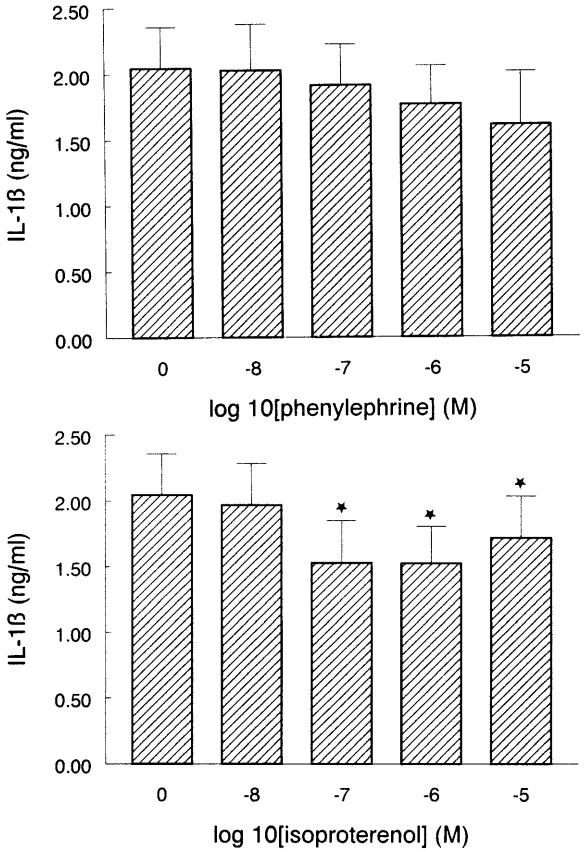

Fig. 3. Effect of increasing concentration of α-adrenergic agonist phenylephrine or β-adrenergic agonist isoproterenol on LPS-induced IL-1β production. Data are means ± SE of 6 different donors. *$P <$ 0.05 vs. LPS only.

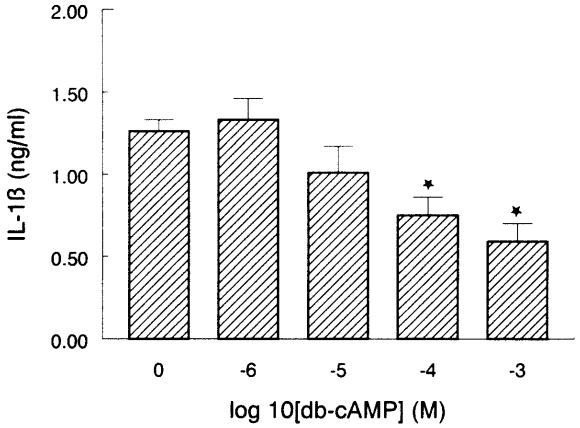

Fig. 4. Dibutyryl-adenosine 3′,5′-cyclic monophosphate (DbcAMP) dose dependently inhibits LPS-induced IL-1β production. Whole blood diluted 1:1 in RPMI-1640 was incubated for 16 h with LPS (10 ng/ml) in presence or absence of increasing concentrations of DbcAMP. Data are means ± SE of 6 different donors. *$P <$ 0.05 vs. LPS only.

Potentiation of IL-10 production contributes to inhibition IL-1β production by epinephrine. IL-10 is known to inhibit LPS-induced IL-1β production (5, 8). It was therefore possible that epinephrine inhibits LPS-induced IL-1β production in whole blood at least in part by enhancing the release of IL-10 (30). To test this hypothesis we incubated whole blood with LPS (10

Table 1. *Epinephrine does not influence LPS-induced IL-1β production in presence of anti-TNF or anti-IL-10*

	IL-1β, ng/ml
Experiment 1 (n = 5)	
LPS	1.94 ± 0.48
LPS + Epi	1.43 ± 0.27*
LPS + anti-TNF	1.42 ± 0.40*
LPS + anti-TNF + Epi	1.26 ± 0.25*†
Experiment 2 (n = 6)	
LPS	1.86 ± 0.40
LPS + Epi	1.42 ± 0.22*
LPS + anti-IL-10	2.21 ± 0.34*†
LPS + anti-IL-10 + Epi	2.20 ± 0.36*†

Values are means ± SE. Whole blood diluted 1:1 in RPMI-1640 was incubated for 16 h with lipopolysaccharide (LPS, 10 ng/ml) in presence or absence of epinephrine (Epi, 10^{-6} M), anti-tumor necrosis factor (TNF, 25 μg/ml), anti-interleukin (IL)-10 (25 μg/ml), and/or irrelevant control monoclonal antibodies (25 μg/ml). *$P <$ 0.05 vs. LPS only. †$P <$ 0.05 vs. LPS + Epi.

ng/ml) in the presence or absence of epinephrine (10^{-6} M), a neutralizing anti-IL-10 MAb (25 μg/ml), or an equivalent amount of an irrelevant isotype-matched control MAb. Anti-IL-10 potentiated LPS-induced IL-1β production (Table 1). In the presence of anti-IL-10, epinephrine did not inhibit IL-1β production. Hence these results suggested that the inhibiting effect of epinephrine on IL-1β production is dependent on the concurrent enhancing effect of epinephrine on IL-10 production.

DISCUSSION

The primary objective of the present study was to examine the effect of epinephrine on IL-1β production in humans. Because the dose of LPS that can be given safely to normal humans in vivo is too low to induce a detectable IL-1β response (30, 31), we chose to investigate the IL-1β production capacity of whole blood obtained from humans infused with epinephrine. The dose of epinephrine sought to resemble two clinically relevant situations, i.e., plasma concentrations of epinephrine were in the same range as those reported in patients with septic shock (12, 30), and the rate and dose at which epinephrine were infused were in the same range as the rate and dose at which this hormone is initiated as part of the treatment of septic patients (15). It is demonstrated that epinephrine infusion was associated with a decreased production of IL-1β by LPS-stimulated whole blood, an effect that lasted for at least 21 h after the start of the infusion.

The mechanisms by which epinephrine influenced IL-1β production was investigated further in whole blood in vitro. We chose to study epinephrine effects in whole blood, rather than in cultures of isolated cells, because the use of whole blood eliminates possible artifacts that may be associated with isolation of cells, such as adherence-induced expression of TNF (14). In addition, the effect of a hormone on cytokine production can be investigated in whole blood under conditions with a physiological endocrine background and in the presence of all blood components, which is likely to be of more relevance for the in vivo situation (4, 29, 30). It should be noted that the concentrations of epinephrine needed in whole blood in vitro were much higher than epinephrine concentrations achieved during the in vivo experiments. Similar epinephrine concentrations were used by our and other groups in in vitro studies examining the effect of this hormone on cytokine production (25, 30). Possibly, epinephrine levels added in vitro rapidly declined due to oxidation. Nonetheless, in whole blood, epinephrine inhibited LPS-induced IL-1β production by an exclusive effect on adrenergic receptors. Indeed, adrenergic blockade by propranolol completely prevented the effect of epinephrine on IL-1β production, and specific receptor adrenergic stimulation reproduced the effect of epinephrine. By contrast, neither the α-receptor antagonist phentolamine nor specific α-adrenergic stimulation influenced IL-1β levels.

Elevation of intracellular cAMP levels is a well-described postreceptor effect of adrenergic stimulation (25, 32). The inhibition of TNF production by β-adrenergic agents has been linked to an increase in intracellular cAMP concentrations (1, 25, 28, 32). The effect of β-adrenergic stimulation on cAMP levels is transient; whereas incubation of mononuclear cells with epinephrine or the β-agonist isoproterenol for 2 h led to a rise in intracellular cAMP concentrations, incubation for 24 h resulted in a decrease in cAMP levels (25). LPS-induced production of TNF paralleled this biphasic change in cAMP levels, i.e., preexposure of mononuclear cells to epinephrine for 3 h reduced TNF synthesis, whereas preincubation with epinephrine for 24 h enhanced TNF synthesis (25). Therefore, in the present study we wished to assess the cytokine production capacity of whole blood after various durations of epinephrine infusions. However, as was found earlier for the sustained ability of epinephrine to inhibit LPS-induced TNF production in vivo and ex vivo (30), IL-1β production was diminished even after exposure to epinephrine for 21 h.

In our study, elevation of intracellular cAMP levels by DBcAMP resulted in a dose-dependent inhibition of LPS-induced IL-1β production by whole blood, providing further evidence that epinephrine mediates its effect on IL-1β synthesis via β-adrenergic stimulation. The effect of increased intracellular cAMP on IL-1 (both IL-1α and IL-1β) production by isolated cells or cell lines is controversial (1, 7, 16, 17, 22, 23, 27, 28). Elevation of cAMP by various agents has been reported either to enhance or not to influence IL-1 mRNA levels (16, 17, 23, 28), and either to enhance, reduce, or not to influence IL-1 protein secretion (1, 7, 16, 17, 22, 23, 27, 28). To our knowledge, our study is the first to study the effect of elevated cAMP levels on IL-1β production in whole blood cultures. It is conceivable that conflicting data on the effect of cAMP on IL-1 production may be related to differences in experimental conditions and/or stimuli to induce IL-1 synthesis. With respect to the latter possibility it is interesting to note that in one study elevated cAMP concentrations inhibited monocytic IL-1β production induced by LPS but enhanced IL-1β production stimulated by phorbol 12-myristate 13-acetate (16).

The present study did not investigate the effect of epinephrine on IL-1 gene transcription and translation. Also, we did not address the effect of epinephrine on intracellular vs. extracellular IL-1 levels, a relevant issue considering the fact that the majority of IL-1 produced by mononuclear cells is retained intracellularly (6).

The production of IL-1β induced by LPS is partly dependent on TNF (11 and the present study). Because epinephrine inhibits LPS-induced TNF production (25, 29, 30), we hypothesized that the inhibition of IL-1β production by epinephrine could in part be secondary to reduced TNF levels. Therefore, to eliminate the effect of reduced TNF concentrations in the presence of epinephrine, experiments with a neutralizing anti-TNF MAb were performed. In the presence of anti-TNF, epinephrine failed to influence IL-1β concentrations in LPS-stimulated whole blood. Furthermore, because IL-10 inhibits LPS-induced IL-1β production (5, 8) and

epinephrine enhances IL-10 release in LPS-stimulated whole blood (29, 30), we argued that the epinephrine-induced inhibition of IL-1β release could have been caused by increased IL-10 levels. We indeed found that anti-IL-10 enhances LPS-induced IL-1β production and that in the presence of anti-IL-10 epinephrine did not affect IL-1β levels. Hence these experiments suggest that epinephrine attenuates IL-1β production in whole blood indirectly via inhibition of TNF and potentiation of IL-10 production.

The systemic inflammatory response syndrome associated with sepsis involves both activation of the immune and the neuroendocrine system. Evidence is accumulating that after an acute infectious challenge epinephrine, either given exogenously or produced endogenously, has anti-inflammatory effects on the cytokine network by inhibiting the release of TNF and enhancing the release of IL-10 (19, 24, 26, 30). We here show that epinephrine inhibits the production of potent proinflammatory cytokine IL-1β, providing further support for the notion that epinephrine may act to dampen excessive proinflammatory effects of cytokines during the early phases of systemic infection.

Perspectives

Systemic infection leads to the activation of multiple host mediator systems. It has become clear that inflammatory responses that originally were considered to occur independently may influence each other. Activation of the cytokine network plays an important role in the immunological consequences of sepsis. Enhanced release of catecholamines in the early phases after an acute injury has attracted much attention from investigators examining the role of stress hormones in the metabolic changes observed in injured patients. By now it is evident that bidirectional interactions exist between the cytokine network and catecholamines. In this study we show that epinephrine inhibits the production of one of the major proinflammatory cytokines IL-1. Taken together with previous studies, the picture emerges that stress hormones, traditionally considered important for the host metabolic response to infection, may play a significant role in the host immune response to infection.

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