

# Lipopolysaccharide-Induced Interleukin 8 Production by Human Whole Blood Is Enhanced by Epinephrine and Inhibited by Hydrocortisone

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**To determine the effect of epinephrine and hydrocortisone on lipopolysaccharide (LPS)-induced interleukin 8 (IL-8) production, human whole blood was stimulated with LPS in the presence or absence of these stress hormones. Epinephrine caused a dose-dependent increase in LPS-induced IL-8 production, which was mediated exclusively via  $\beta$ -adrenergic receptors, as reflected by the facts that  $\beta$  (but not  $\alpha$ ) receptor blockade reversed the epinephrine effect and  $\beta$  (but not  $\alpha$ ) receptor stimulation reproduced the epinephrine effect. Further, elevating cellular cyclic AMP (cAMP) concentrations, a known effect of  $\beta$ -adrenergic stimulation, by addition of dibutyryl cAMP also enhanced LPS-induced IL-8 production. Epinephrine-induced upregulation of IL-10 production masked an even more pronounced stimulating effect of this hormone on IL-8 synthesis, as indicated by the finding that the extent of IL-8 upregulation was greater in the presence of anti-IL-10 than in the absence of anti-IL-10. Hydrocortisone dose-dependently inhibited LPS-induced IL-8 production and reversed epinephrine-induced enhancement of IL-8 production. Epinephrine and hydrocortisone have opposite effects on IL-8 production, which may be relevant for the understanding of endogenous and therapeutic stress hormone influences on IL-8 mediated inflammation.**

Interleukin 8 (IL-8) is a 6- to 8-kDa cytokine that can be produced by a large variety of cell types, including monocytes, macrophages, neutrophils, and endothelial cells, after stimulation with many different agonists (1, 16). Enhanced production of IL-8 has been reported for a number of localized and systemic inflammatory diseases, including pneumonia, the adult respiratory distress syndrome, and sepsis (3, 9, 10, 19). In these conditions, IL-8 may be an important regulatory factor in neutrophil-mediated inflammation. IL-8 induces the complete spectrum of responses observed in chemotactically stimulated neutrophils; i.e., it activates the motile apparatus and directional migration and it induces expression of surface adhesion molecules, production of reactive oxygen metabolites, and degranulation (1, 16). Locally produced IL-8 is considered to be important for the recruitment and activation of neutrophils into inflamed tissue compartments (4, 12).

In recent years it has become clear that stress hormones can influence the production of cytokines. In healthy humans injected with lipopolysaccharide (LPS), glucocorticoids and catecholamines can inhibit the production of the proinflammatory cytokine tumor necrosis factor alpha (TNF- $\alpha$ ), while simultaneously enhancing the production of the anti-inflammatory cytokine IL-10 (17, 18). Hence, these stress hormones may exert a net anti-inflammatory effect on the cytokine network. Little is known about the effect of stress hormones on the production of IL-8.

The primary objective of the present study was to determine the effects of epinephrine and hydrocortisone on IL-8 production. Knowledge of such effects is relevant not only for the understanding of endogenous stress hormone influences on

IL-8 synthesis during inflammation but also for the therapeutic use of exogenous glucocorticoids and  $\beta$ -adrenergic agents in patients with pulmonary or systemic inflammatory conditions.

## MATERIALS AND METHODS

**Reagents.** LPS (*Escherichia coli* serotype 0127:B8) was purchased from Sigma (St. Louis, Mo.). Whole-blood stimulations were carried out in the presence or absence of the following agents: epinephrine (Parke-Davis, Morris Plains, N.J.), phenolamine (CIBA-GEIGY, Basel, Switzerland), propranolol (Ayerst, Philadelphia, Pa.), phenylephrine (American Regent Laboratories, Shirley, N.Y.), isoproterenol (Sanofi Winthrop Pharmaceuticals, New York, N.Y.), terbutaline (CIBA-GEIGY), UK-14,304 (kindly provided by Pfizer Limited, Sandwich, United Kingdom), cortisol (hydrocortisone sodium succinate; Abbott Laboratories, North Chicago, Ill.), dibutyryl-cyclic AMP (db-cAMP; Sigma Chemical Co.), a neutralizing anti-human IL-10 monoclonal antibody (MAb; IF9; Medgenix, Fleurus, Belgium), and anti-human follicle-stimulating hormone (isotype-matched control antibody; kindly provided by Arnaud Marchant, Free University of Brussels, Brussels, Belgium).

**Whole-blood stimulation.** Whole-blood stimulation was performed as described previously (17, 18). Briefly, blood was collected aseptically from healthy subjects with a sterile collecting system consisting of a butterfly needle connected to a syringe (Becton Dickinson & Co., Rutherford, N.J.). Anticoagulation was obtained by using sterile heparin (Elkins-Sinn Inc., Cherry Hill, N.J.; 10 U of blood per ml, final concentration). Whole blood, diluted 1:1 in sterile RPMI 1640 supplemented with L-glutamine (Gibco-BRL, Life Technologies Inc., Grand Island, N.Y.), was stimulated for 4 to 24 h at 37°C with LPS (10 ng/ml, final concentration) in sterile polypropylene tubes (Becton Dickinson & Co.). For these experiments, polypropylene tubes were pre-filled with 0.75 ml of RPMI 1640 containing the appropriate concentrations of LPS, hormones and/or adrenergic or antiadrenergic agents, after which 0.75 ml of heparinized blood was added. The 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. Baseline hormone levels and leukocyte counts were not measured since comparisons were made between blood samples, with or without exogenously added hormones and/or other compounds, drawn from the same individual at the same time. Hence, baseline hormone levels and leukocyte counts were identical in all tubes of samples obtained from one donor, and the statistical analysis was performed by using a Wilcoxon test for matched pairs (see below).

**Assay.** IL-8 was measured by enzyme-linked immunosorbent assay (Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, CLB, Amsterdam, The Netherlands) strictly according to the instructions of the manufacturer. Briefly, polystyrene microtiter wells were coated overnight at 4°C with

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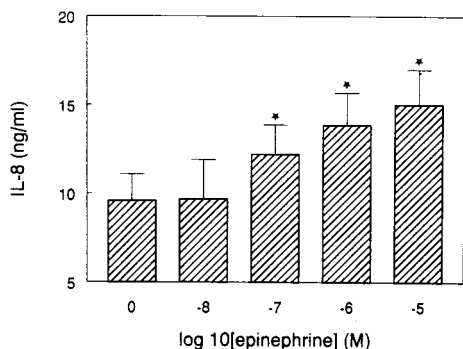


FIG. 1. Epinephrine dose-dependently enhances LPS-induced IL-8 production. Whole blood diluted 1:1 in RPMI 1640 was incubated for 16 h with LPS (10 ng/ml) in the presence or absence of increasing concentrations of epinephrine. Data are means  $\pm$  standard errors for six different donors.  $\star$ ,  $P < 0.05$  versus LPS only.

a murine anti-human IL-8 MAb (clone IL-8.1) (10) at 1  $\mu$ g/ml. After the plates were washed and blocked, samples and standards were added for 1 h at 37°C. The standard used was natural human IL-8 which was calibrated against the World Health Organization (WHO) interim international standard (IL-8 89/520; National Institute for Biological Standards and Control, Pottery Bar, Hertfordshire, United Kingdom; 1 WHO U = 10 ng of IL-8). Biotinylated sheep anti-human IL-8 and streptavidin-horseradish peroxidase conjugate were used for detection. The detection limit of the assay was 5 pg/ml. The assay has no cross-reactivity with 25 different recombinant human cytokines, chemokines, and growth factors.

**Statistical analysis.** All values are given as means  $\pm$  standard errors of the means. Data were compared by using the Wilcoxon test for matched samples. A  $P$  of  $<0.05$  was considered to represent a statistically significant difference.

## RESULTS

**Epinephrine enhances IL-8 production.** Epinephrine caused a dose-dependent increase in IL-8 production by whole blood incubated with LPS for 16 h (Fig. 1). This enhancing effect was not dependent on the duration of LPS stimulation, since in the presence of epinephrine elevated IL-8 concentrations were detected after incubation periods varying between 4 and 24 h (Fig. 2). Since epinephrine binds to both  $\alpha$  ( $\alpha_1$ - and  $\alpha_2$ -) and  $\beta$  ( $\beta_1$ - and  $\beta_2$ -) adrenergic receptors, we next assessed which adrenergic receptor was involved in the effects of epinephrine on IL-8 production. For this purpose, we incubated whole blood with LPS (10 ng/ml) in the presence or absence of epinephrine ( $10^{-6}$  M), the  $\alpha$  ( $\alpha_1$ - and  $\alpha_2$ -) adrenergic receptor antagonist phentolamine ( $10^{-5}$  M), and/or the  $\beta$  ( $\beta_1$ - and  $\beta_2$ -)

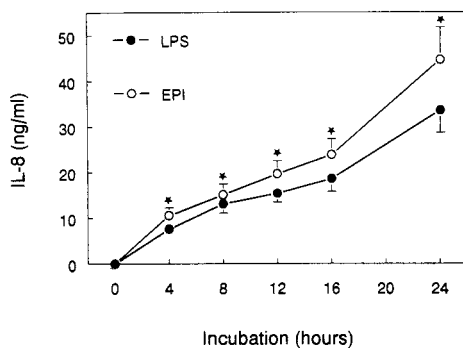


FIG. 2. Epinephrine enhances IL-8 production irrespective of the duration of incubation of whole blood with LPS. Whole blood diluted 1:1 in RPMI 1640 was incubated for 4 to 24 h with LPS (10 ng/ml) in the presence or absence of epinephrine (EPI;  $10^{-6}$  M). Data are means  $\pm$  standard errors for eight different donors.  $\star$ ,  $P < 0.05$  versus LPS only.

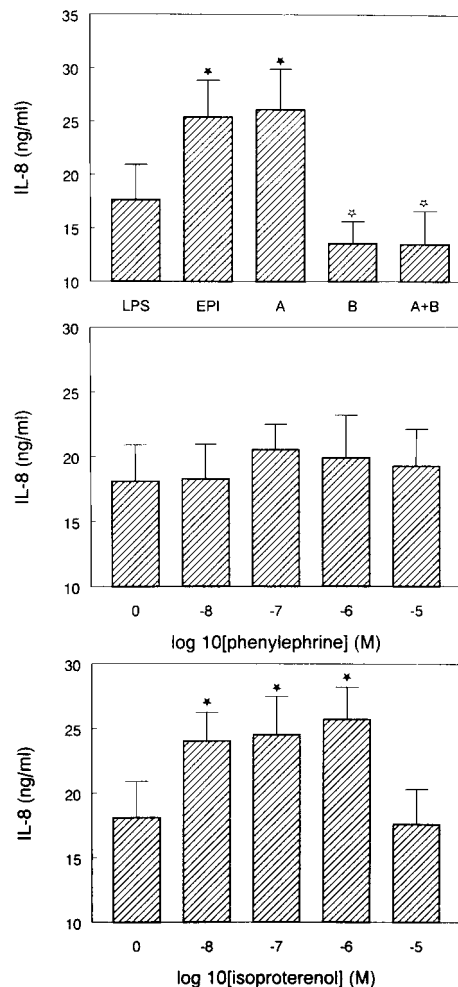


FIG. 3. Effect of  $\alpha$  and/or  $\beta$  receptor blockade and of  $\alpha$  or  $\beta$  receptor stimulation on IL-8 production by LPS-stimulated whole blood. Whole blood diluted 1:1 in RPMI 1640 was incubated for 16 h with LPS (10 ng/ml). Results from the following incubations are shown in the upper panel: LPS, incubation with LPS only; EPI, incubation with epinephrine ( $10^{-6}$  M); A, incubation with epinephrine ( $10^{-6}$  M) and the  $\alpha_1$  and  $\alpha_2$  antagonist phentolamine ( $10^{-5}$  M); B, incubation with epinephrine ( $10^{-6}$  M) and the  $\beta_1$  and  $\beta_2$  antagonist propranolol ( $10^{-5}$  M); A+B, incubation with epinephrine, phentolamine, and propranolol. The lower panels show the effect of increasing concentrations of the  $\alpha$ -adrenergic agonist phenylephrine or the  $\beta$ -adrenergic agonist isoproterenol. Data are means  $\pm$  standard errors for six different donors. Solid star,  $P < 0.05$  versus LPS only. Open star,  $P < 0.05$  versus LPS with epinephrine.

adrenergic receptor antagonist propranolol ( $10^{-5}$  M). Incubation with phentolamine or propranolol only (i.e., without epinephrine) did not influence LPS-induced IL-8 production (data not shown). Blockade of  $\alpha$  receptors by phentolamine did not influence the epinephrine stimulation of IL-8 production. By contrast, propranolol completely prevented this effect (Fig. 3). To confirm that  $\beta$ -adrenergic receptor stimulation mediates the upregulation of LPS-induced IL-8 production, we next incubated whole blood with LPS and specific  $\alpha$ - or  $\beta$ -adrenergic agonists. As depicted in Fig. 3, isoproterenol ( $\beta_1$  plus  $\beta_2$  receptor agonist) was a potent stimulator of LPS-induced IL-8 release. Also, terbutaline (a  $\beta$  receptor agonist with predominant affinity for the  $\beta_2$  receptor) increased LPS-induced IL-8 levels (data not shown). By contrast, phenylephrine (an  $\alpha$  receptor agonist with predominant affinity for the  $\alpha_1$  receptor) did not influence IL-8 levels (Fig. 3). Further, a specific  $\alpha_2$

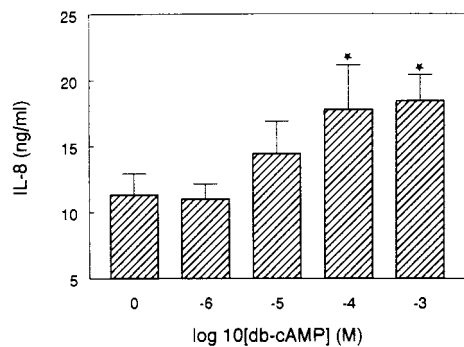


FIG. 4. db-cAMP dose-dependently enhances LPS-induced IL-8 production. Whole blood diluted 1:1 in RPMI 1640 was incubated for 16 h with LPS (10 ng/ml) in the presence or absence of increasing concentrations of db-cAMP. Data are means  $\pm$  standard errors for six different donors.  $\star$ ,  $P < 0.05$  versus LPS only.

receptor agonist (UK-14,304) did not alter LPS-induced IL-8 production (data not shown).

**db-cAMP enhances IL-8 production.** Since  $\beta$ -adrenergic stimulation is known to result in an elevation of intracellular cAMP levels (14, 20), we were interested to determine the effect of db-cAMP on IL-8 production. The addition of db-cAMP caused a dose-dependent increase in IL-8 levels in LPS-stimulated whole blood (Fig. 4).

**Effect of anti-IL-10 on epinephrine-induced enhancement of IL-8 production.** We have shown previously that epinephrine stimulates LPS-induced IL-10 production in human whole blood (17). It has been demonstrated that IL-10 can inhibit IL-8 production (7, 8). Enhancement of IL-10 production by epinephrine could therefore mask an even more pronounced potentiating effect on IL-8 production by epinephrine. To evaluate this possibility, we incubated whole blood for various time periods with LPS (10 ng/ml) in the presence or absence of epinephrine ( $10^{-6}$  M), a neutralizing anti-IL-10 MAb (25  $\mu$ g/ml), or an equivalent amount of an irrelevant isotype-matched control MAb. Anti-IL-10 potentiated LPS-induced IL-8 production, an effect that became significant after incubations of whole blood for 24 h (Table 1). The extent of IL-8 stimulation was greater in the presence of anti-IL-10 than in the absence of anti-IL-10 (Table 1).

**Hydrocortisone inhibits LPS-induced IL-8 production.** Hydrocortisone caused a dose-dependent inhibition of IL-8 production by LPS-stimulated whole blood (Fig. 5). Further, hy-

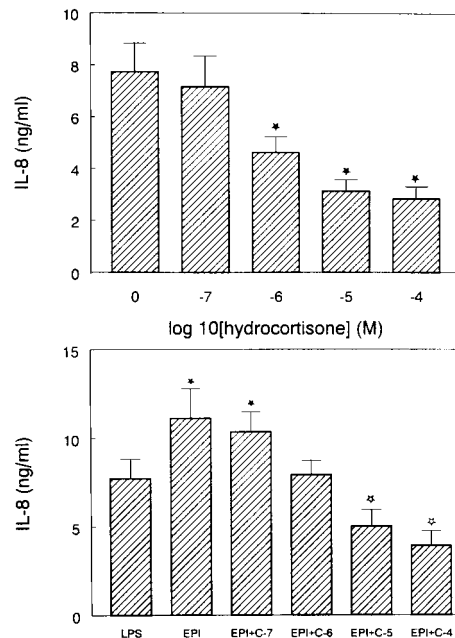


FIG. 5. Effect of hydrocortisone on IL-8 concentrations in LPS-stimulated whole blood. (Upper panel) Whole blood diluted 1:1 in RPMI 1640 was incubated for 16 h with LPS (10 ng/ml) in the presence or absence of increasing concentrations of hydrocortisone. (Lower panel) Whole blood diluted 1:1 in RPMI 1640 was incubated for 16 h with LPS (10 ng/ml) in the presence or absence of epinephrine with or without increasing concentrations of hydrocortisone. EPI, epinephrine ( $10^{-6}$  M); EPI+C-N, epinephrine ( $10^{-6}$  M) plus hydrocortisone ( $10^{-N}$  M). Data are means  $\pm$  standard errors for six different donors. Solid star,  $P < 0.05$  versus LPS only; open star,  $P < 0.05$  versus LPS plus epinephrine.

drocortisone inhibited the upregulation of LPS-induced IL-8 production by epinephrine (Fig. 5).

## DISCUSSION

Previous research has established that both epinephrine and hydrocortisone inhibit LPS-induced TNF production by whole blood in vitro (2, 14, 17, 18). We demonstrate here that these stress hormones have opposite effects on the production of IL-8 in LPS-stimulated whole blood; i.e., epinephrine enhanced IL-8 production, while hydrocortisone reduced IL-8 levels.

Epinephrine potentiated LPS-induced IL-8 production by having an effect on  $\beta$ -adrenergic receptors. Indeed,  $\beta$ -adrenergic blockade by propranolol completely prevented the effect of epinephrine on IL-8 production, and specific  $\beta$  receptor adrenergic stimulation reproduced the effect of epinephrine. By contrast, neither the  $\alpha$  receptor antagonist phentolamine nor specific  $\alpha$ -adrenergic stimulation altered IL-8 levels. It should be noted that the effects of epinephrine on cytokine production are not solely mediated by  $\beta$ -adrenergic receptors. We have previously shown that epinephrine upregulates LPS-induced IL-10 production by a combined effect on  $\alpha$  and  $\beta$  receptors (18).

Although our data do not prove that IL-8 production is positively regulated by cAMP, the results do suggest that such a mechanism exists. Indeed, the elevation of intracellular cAMP levels, a well-described postreceptor effect of  $\beta$ -adrenergic stimulation, by incubation with the cAMP analog db-cAMP was associated with a dose-dependent increase in IL-8 concentrations in whole blood exposed to LPS. In an earlier

TABLE 1. Effect of anti-IL-10 MAb on epinephrine-induced stimulation of IL-8 production by LPS-stimulated whole blood<sup>a</sup>

Incubation time (h)	IL-8 level <sup>b</sup> (ng/ml) in the presence of:			
	LPS	LPS + EPI	LPS + anti-IL-10	LPS + EPI + anti-IL-10
4	7.88 $\pm$ 1.64	12.49 $\pm$ 2.37 <sup>c</sup>	6.85 $\pm$ 1.23	10.26 $\pm$ 2.02 <sup>d</sup>
8	15.45 $\pm$ 3.68	20.61 $\pm$ 6.07 <sup>c</sup>	17.69 $\pm$ 4.63	19.19 $\pm$ 3.62 <sup>d</sup>
16	25.40 $\pm$ 8.43	36.37 $\pm$ 13.47 <sup>c</sup>	31.40 $\pm$ 11.43	58.08 $\pm$ 20.94 <sup>d</sup>
24	41.50 $\pm$ 12.52	60.29 $\pm$ 20.64 <sup>c</sup>	67.31 $\pm$ 23.27 <sup>c</sup>	121.22 $\pm$ 49.91 <sup>d</sup>

<sup>a</sup> Whole blood diluted 1:1 in RPMI 1640 was incubated for 4 to 24 h with LPS (10 ng/ml) in the presence or absence of epinephrine (EPI;  $10^{-6}$  M), anti-IL-10 MAb (25  $\mu$ g/ml), and/or an irrelevant control MAb (25  $\mu$ g/ml).

<sup>b</sup> Levels are means  $\pm$  standard errors for six different donors.

<sup>c</sup>  $P < 0.05$  versus LPS only (after the same incubation period).

<sup>d</sup>  $P < 0.06$  versus LPS plus anti-IL-10 (after the same incubation period).

study, prostaglandin E<sub>2</sub>, an inflammatory mediator known to elevate intracellular cAMP levels, was reported to inhibit LPS-induced IL-8 production by isolated human monocytes (15). A clear explanation for this apparent discrepancy with the current results is not readily available, especially since it has been established that mononuclear cells are by far the most important producers of IL-8 in LPS-stimulated whole blood (6) and that forskolin, another cAMP-increasing agent, can induce accumulation of IL-8 mRNA (13). Conceivably, suppression of IL-8 production by prostaglandin E<sub>2</sub> is not mediated by alterations in cAMP concentrations.

In accordance with studies by DeForge et al. (5, 6), IL-8 production in LPS-stimulated whole blood followed biphasic kinetics, reaching a plateau after incubations of 6 to 12 h, with IL-8 concentrations increasing again after incubations of longer durations. The second wave of IL-8 production has been found to be mediated in part by TNF and IL-1 produced within the whole-blood system (5, 6). Since IL-10 can inhibit IL-8 production triggered by LPS (7, 8) and since we had found previously that epinephrine upregulates IL-10 production in LPS-stimulated whole blood (18), we were interested to evaluate the role of endogenous IL-10 in LPS-induced IL-8 production in the presence and absence of epinephrine. It was demonstrated that incubation with anti-IL-10 was associated with increased IL-8 concentrations in whole blood after incubation with LPS for 24 h, indicating that endogenous IL-10 inhibits the second wave of IL-8 release. Further, the extent of the epinephrine-induced increase in IL-8 levels was more pronounced after elimination of endogenous IL-10, suggesting that the upregulation of LPS-induced IL-10 by epinephrine conceals an even stronger stimulation of IL-8 release by this hormone.

Our finding of dose-dependent inhibition of LPS-induced IL-8 production in whole blood by hydrocortisone confirms earlier studies in which dexamethasone reduced IL-8 synthesis by LPS-stimulated monocytes (13, 15). We further showed that hydrocortisone can reverse epinephrine-induced upregulation of IL-8 production. Notably, we previously reported that hydrocortisone also abrogated epinephrine-induced enhancement of IL-10 production and that these stress hormones additively inhibit the synthesis of TNF (17).

We specifically chose to study the effects of epinephrine and hydrocortisone on IL-8 production in whole blood rather than in cultures of isolated cells or cell lines. The use of whole blood eliminates possible artifacts that may be associated with isolation of cells, such as adherence-induced expression of TNF (11). Additionally, by using whole blood the effect of a hormone on the release of cytokines can be investigated against 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. It should be noted, however, that cellular and/or molecular mechanisms underlying the effects observed cannot be addressed thoroughly in whole blood.

Knowledge of the effects of stress hormones on IL-8 production may be important for the understanding of interactions between neuroendocrine activation and neutrophil-mediated inflammation. Moreover, administration of  $\beta$ -adrenergic agents and/or glucocorticoids frequently is part of the treatment of patients with systemic or local inflammation. We demonstrate here that epinephrine enhances LPS-induced production of IL-8 in human whole blood via stimulation of the  $\beta$ -adrenergic receptor, an effect that can be reversed by coincubation with hydrocortisone. Further studies are warranted to establish the

impact of these effects on IL-8-mediated neutrophil responses during inflammation.

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