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Interleukin-1-Induced Nonspecific Resistance to Bacterial Infection in Mice Is Not Mediated by Glucocorticosteroids

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Preexposure to a low dose of interleukin-1 (IL-1; 3 to 30 µg/kg) 24 h before a lethal gram-negative bacterial infection prolonged survival in normal and granulocytopenic mice. To examine whether this protective effect is mediated by glucocorticosteroids, we first measured corticosterone concentrations in mice after administration of 80 and 800 ng of IL-1. IL-1 induced a dose-dependent increase in corticosterone levels in plasma. Next, the corticosterone peak induced by a protective dose of IL-1 (800 ng) was simulated by administration of synthetic human adrenocorticotrophic hormone 1-24 (ACTH) in normal and neutropenic mice. Although corticosterone levels induced by pretreatment with IL-1 or ACTH were virtually identical, the ACTH-induced corticosterone peak was not associated with protection against *Klebsiella pneumoniae* infection in normal mice and *Pseudomonas aeruginosa* infection in neutropenic mice. This indicates that the protective effect of IL-1 pretreatment against gram-negative bacterial infection is not mediated by elevated levels of glucocorticosteroids. In addition, we found that plasma corticosterone concentrations during *K. pneumoniae* infection were significantly lower after pretreatment with IL-1 than after pretreatment with ACTH or vehicle, probably reflecting the better physical condition of IL-1-treated mice.

Interleukin-1 (IL-1), a 17-kDa protein produced by many different types of cells, has a variety of immunologic and inflammatory effects (9). When injected into experimental animals, IL-1 is able to enhance nonspecific resistance to several gram-positive and gram-negative bacteria, fungi, and plasmodia (30). For example, we have shown that treatment with a single low dose (80 to 800 ng) of recombinant human IL-1β (rhIL-1β) 24 h before a lethal challenge with gram-negative bacteria prolongs survival in normal and granulocytopenic mice (24, 25). The mechanism of the protective effect of IL-1 has not been elucidated. A direct antimicrobial effect of IL-1 has been excluded in vitro (25). Whether IL-1 induces enhanced clearance of microorganisms in vivo is controversial (13, 14, 24, 25, 27). The presence of a protective effect of IL-1 to infectious challenges in granulocytopenic mice provides evidence for the lack of a major role of neutrophils (13, 25, 27, 30). The lack of effect of pretreatment with cyclo-oxygenase inhibitors or recombinant cytokines on the ability of mice to survive infection also indicates that the induction of cyclo-oxygenase metabolites or cytokines like IL-6, IL-8, or tumor necrosis factor alpha by IL-1 likely does not account for the IL-1-induced resistance (24-26, 28-30).

Injection of IL-1 into mice activates the pituitary-adrenal axis; this is manifested by increased levels of adrenocorticotrophic hormone (ACTH) and corticosterone in plasma (5). The fact that administration of glucocorticosteroids has been shown to increase survival of septic animals (17, 21) raises the question of whether the protective effect of IL-1 might be due to IL-1-induced enhanced secretion of these hormones. To address this issue, we measured the corticosterone responses induced by different dosages of rhIL-1β. Furthermore, we simulated the IL-1-induced corticosterone peaks by administration of synthetic human ACTH_[1-24] (ACTH)

and assessed the effect of administration of ACTH on survival in infected normal and neutropenic mice. To find out whether protection was associated with changes in plasma corticosterone concentrations, we measured postinfectious corticosterone concentrations in mice treated with IL-1 or ACTH as well.

(Part of this report was presented at the Third International Workshop on Cytokines, 10 to 14 November 1991, Stresa, Italy [28a].)

MATERIALS AND METHODS

Mice. Female outbred Swiss mice (weight, 30 to 40 g; TNO, Rijswijk, The Netherlands) were kept under specific-pathogen-free conditions in an artificially lighted room with a light-dark cycle of 12 h (lights on at 7 a.m., lights off at 7 p.m.). For experiments in which corticosterone levels were measured, the mice were housed individually for 4 to 5 days prior to initiation of the studies. Standard lab chow (RMH-TM; Hope Farms, Woerden, The Netherlands) and acidified water were available ad libitum. Granulocytopenic mice received irradiated food.

Materials. rhIL-1β was kindly provided by P. Graber (Glaxo, Geneva, Switzerland) and P. Ghiara (Sclavo, Siena, Italy). According to the specifications of the suppliers, endotoxin contamination was negligible (<1.53 and <1.2 ng/mg, respectively). IL-1 was stored undiluted at -70°C and was diluted immediately before use in pyrogen-free isotonic phosphate-buffered saline (pH 7.4). Inactivated IL-1 was prepared by heating IL-1 at 95°C for 30 min. Human ACTH_[1-24] (Synacthen; CIBA-GEIGY, Arnhem, The Netherlands) was diluted in pyrogen-free saline. To all solutions, including control treatments (saline), normal mouse serum was added to an end volume of 2% (vol/vol). Gentamicin was purchased from Schering, Kenilworth, N.J. Cyclophosphamide (ASTA Pharma, Frankfurt, Germany) was dissolved in sterile pyrogen-free distilled water. Bacterial challenges

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(*Klebsiella pneumoniae* ATCC 43816 and *Pseudomonas aeruginosa* ATCC 27853) were prepared by appropriate dilution of overnight cultures, and cultures were washed three times in saline.

Experimental procedures. All experiments started at 9:30 a.m. (time zero).

(i) **Corticosterone levels after treatment with IL-1 or ACTH.** For single treatments, mice received 80 or 800 ng of IL-1 intraperitoneally (i.p.), 50 μ g of ACTH subcutaneously (s.c.), or vehicle s.c. at time zero. In experiments in which two treatments with 50 μ g of ACTH s.c. were given, these injections were administered at time zero and 1.5 h. In these experiments, mice that were treated with IL-1 i.p. or vehicle s.c. at time zero received vehicle s.c. at 1.5 h. For four treatments with 50 μ g of ACTH, the injections were given at 0, 1.5, 6, and 10 h. In these experiments, mice treated with IL-1 or vehicle at time zero received vehicle at the other time points. At various time points after the first injection, mice were decapitated and blood was collected in EDTA-coated tubes. Plasma was stored at -20°C until it was assayed. For corticosterone measurements in neutropenic mice, neutropenia ($<0.5 \times 10^9$ polymorphonuclear leukocytes per liter) was induced by two s.c. injections of cyclophosphamide (150 mg/kg on day -3 and 100 mg/kg on day 0, before the treatments described above).

(ii) **Effects of IL-1 and ACTH pretreatment on survival.** For survival experiments, some mice were rendered neutropenic as described above. Pretreatments with IL-1, ACTH (one, two, or four administrations), or vehicle were given as described above. The infectious challenge was administered 24 h after the first injection. Nongranulocytopenic mice received *K. pneumoniae* intramuscularly (i.m.) (1×10^6 to 5×10^6 CFU per mouse), whereas granulocytopenic mice received *P. aeruginosa* i.m. (0.5×10^8 to 1×10^8 CFU per mouse). Six hours after the challenge, 120 mg of gentamicin per kg of body weight was given s.c. in order to postpone the time of death and thus accentuate the differences between treatment groups. Mortality was recorded for a period of at least 48 h after challenge.

(iii) **Effects of IL-1 and ACTH pretreatment on corticosterone levels during infection.** For corticosterone measurements during infection, nonneutropenic mice were pretreated 24 h before the challenge with either 800 ng of IL-1 or two doses of 50 μ g of ACTH or vehicle as described above. *K. pneumoniae* (1×10^6 to 5×10^6 CFU per mouse) was administered i.m.; this was followed 6 h later by treatment with 120 mg of gentamicin per kg s.c. Plasma for corticosterone measurements was collected at various time points after the infectious challenge, and the mortality and physical condition of the mice were observed.

Assays. Corticosterone concentrations in plasma were determined by a specific and sensitive radioimmunoassay described by Sweep et al. (20).

Statistical analysis. Survival curves were analyzed by the log rank test (16). Comparisons of medians of corticosterone levels between treatment groups were made by the Kruskal Wallis test at each time point (11). *P* values of <0.05 were considered statistically significant.

RESULTS

Corticosterone levels after IL-1 treatment. The corticosterone response (median values) in nonneutropenic mice to i.p. injection of 80 and 800 ng of IL-1 is shown in Fig. 1A. Plasma corticosterone levels peaked (3.17 μ mol/liter) 2 h after injection of 80 ng of IL-1, and the concentration returned to

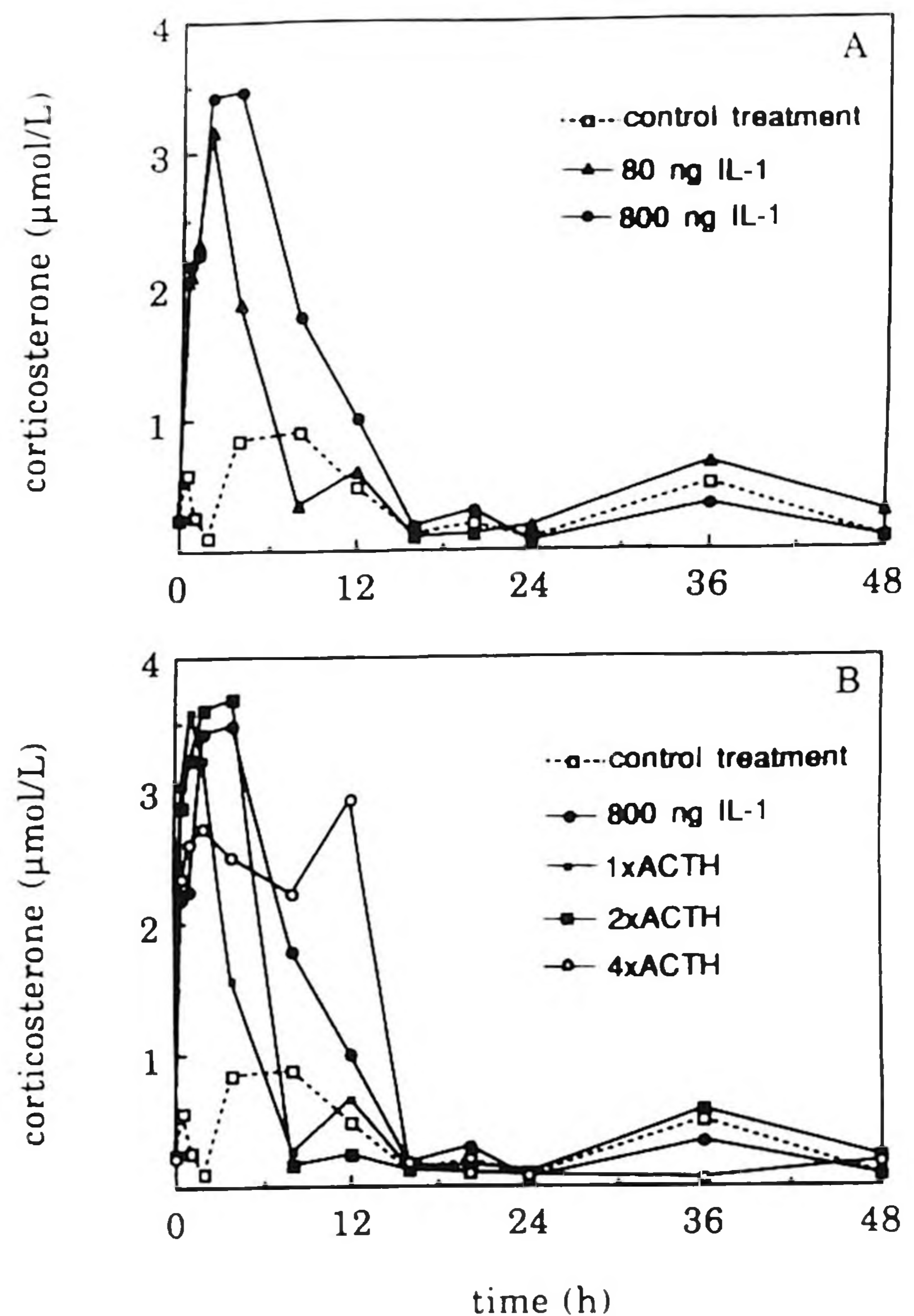


FIG. 1. (A) Median plasma corticosterone values in normal mice after injection of 80 or 800 ng of rhIL-1 β i.p. at time zero (six mice per datum point). Differences between the group treated with 80 ng of IL-1 and the control treatment group were significant at 1, 2, and 4 h after injection ($P = 0.007$, 0.001 , and 0.01 , respectively). Differences between the group treated with 800 ng of IL-1 and the control treatment group were significant at 0.5, 1, 2, and 4 h after injection ($P = 0.05$, 0.002 , 0.03 , and 0.0005 , respectively). The difference between groups treated with 80 ng of IL-1 and 800 ng of IL-1 was significant at 4 h after injection ($P = 0.0001$). (B) Median plasma corticosterone levels after injection of 800 ng of rhIL-1 β i.p. at time zero or one, two, or four s.c. injections of 50 μ g of ACTH $_{[1-24]}$ or control treatment at time zero and 1.5, 6, and 10 h (six mice per datum point). Differences between groups treated with 800 ng of IL-1 and one injection of ACTH were significant at 1, 4, and 8 h after injection ($P = 0.002$, 0.004 , and 0.006 , respectively). The difference between groups treated with 800 ng of IL-1 and two injections of ACTH was significant at 8 h ($P = 0.02$). The difference between groups treated with 800 ng of IL-1 and four injections of ACTH was significant at 12 h ($P = 0.002$).

control levels at 8 h. The differences with the vehicle-treated group reached statistical significance at 1, 2, and 4 h after injection. Plasma corticosterone levels after injection of 800 ng of IL-1 peaked 4 h after injection (3.48 μ mol/liter) and returned to control levels at 16 h. Significant differences with vehicle-treated mice were present at 0.5, 1, 2, and 4 h after IL-1 injection. A significant difference between the groups treated with 80 and 800 ng of IL-1 was present 4 h after injection.

In neutropenic mice, corticosterone levels after administration of 800 ng of IL-1 peaked at 2 h after injection (2.89 μ mol/liter) and returned to the values for control mice at 12 h. Significant differences with vehicle-treated neutropenic mice were present at 1, 1.5, 2, and 4 h after injection. The

corticosterone levels induced by IL-1 or four injections of ACTH in neutropenic mice did not differ significantly at any time point (data not shown).

The circadian rhythm of corticosterone levels observed in plasma of mice treated with vehicle was similar to that in plasma of untreated mice reported by others (10). The low basal corticosterone levels in vehicle-treated mice indicate that blood sampling took place under relatively stress-free circumstances.

Simulation of IL-1-induced increased corticosterone levels by administration of ACTH. Corticosterone concentrations (median values) in plasma after administration of 800 ng of IL-1 and after one, two, or four consecutive injections of 50 μ g of ACTH in normal mice are depicted in Fig. 1B. Plasma corticosterone levels after one injection of ACTH peaked at 1 h after injection (3.59 μ mol/liter) and reached levels not significantly different from those in control mice at 8 h.

The corticosterone levels after two injections of ACTH were not significantly different from the levels induced by IL-1, with the exception of the value obtained 8 h after injection, at which time point corticosterone levels were significantly higher after IL-1 administration. Four injections of ACTH produced a corticosterone peak which lasted longer than the IL-1-induced peak, the ACTH-induced level being significantly greater than the IL-1-induced level 12 h after injection. When the same regimen of 800 ng of IL-1 or four ACTH injections was administered to neutropenic mice, plasma corticosterone concentration curves did not differ significantly at any time point (data not shown). After i.p. injection of 0.1 ml of IL-1 vehicle with 800 ng of heat-inactivated IL-1 and s.c. injection of 0.2 ml of saline, similar corticosterone levels were observed (data not shown). This indicates that differences in the route of administration, injection volume, and vehicles for treatment with IL-1 versus ACTH or control therapy do not induce different corticosterone responses. Since additional s.c. vehicle injections also did not significantly alter corticosterone levels, only the levels of the i.p. control group are presented in Fig. 1B.

In infection experiments, two and four doses of ACTH were used to induce corticosterone responses.

Effect of IL-1 and ACTH on survival. Pretreatment of normal mice with 800 ng of IL-1 24 h before an i.m. infection with *K. pneumoniae* significantly enhanced survival (Fig. 2A). To investigate whether this protective effect was mediated by the enhanced plasma corticosterone level induced by IL-1, the effect of two ACTH doses on survival was assessed. Despite the similar corticosterone patterns after IL-1 and ACTH treatments, the protective effect of IL-1 could not be reproduced by ACTH administration (Fig. 2A). When these treatments were given to granulocytopenic mice before an i.m. *P. aeruginosa* infection, IL-1 enhanced survival significantly, while ACTH had no effect at all compared with the effect of control therapy (Fig. 2B).

When four doses of ACTH were administered, which produced larger corticosterone peaks than those produced with IL-1, no protection was observed in normal mice infected with *K. pneumoniae* (Fig. 2C) or granulocytopenic mice infected with *P. aeruginosa* (Fig. 2D).

Effect of IL-1 and ACTH pretreatment on corticosterone levels during infection. Mice were infected with *K. pneumoniae* after pretreatment with 800 ng of IL-1, two doses of 50 μ g of ACTH, or vehicle injection. As expected, approximately 20% of control and ACTH-treated mice died during the experiment, while all of the IL-1-treated mice survived for 48 h. Plasma corticosterone levels were increased for 6 to

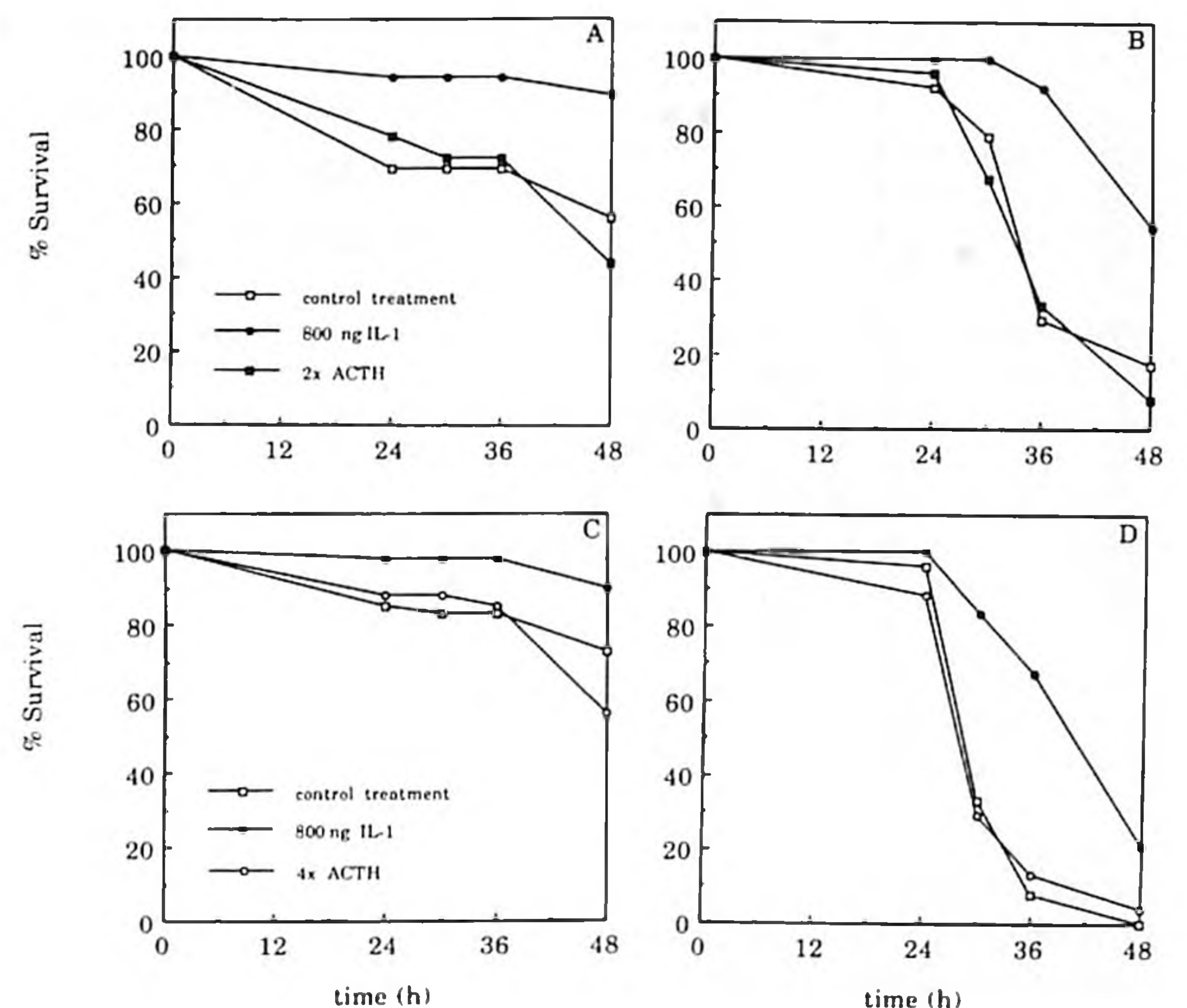


FIG. 2. (A) Survival of normal mice infected i.m. at time zero with *K. pneumoniae* after pretreatment at -24 h with 800 ng of rhIL-1 β i.p., two doses of ACTH $_{[1-24]}$ s.c., or vehicle s.c. at -24 and -22.5 h (36 mice per group). Differences between IL-1-treated and control mice were significant ($\chi^2 = 8.56$; $P < 0.01$). Differences between ACTH-treated and control mice were not significant. (B) The same experiment as described for panel A in granulocytopenic mice infected i.m. with *P. aeruginosa* (24 mice per group). Differences between IL-1-treated and control mice were significant ($\chi^2 = 9.94$; $P < 0.005$), whereas differences between ACTH-treated and control mice were not significant. (C) Survival of normal mice infected i.m. with *K. pneumoniae* at time zero after pretreatment at -24 h with 800 ng of rhIL-1 β i.p. or four doses of ACTH $_{[1-24]}$ or control treatment s.c. at -24 , -22.5 , -18 , and -14 h (48 mice per group). Differences between IL-1-treated and control mice were significant ($\chi^2 = 4.30$; $P < 0.05$). Differences between ACTH-treated and control mice were not significant. (D) The same experiment as described for panel C in granulocytopenic mice infected i.m. with *P. aeruginosa* (24 mice per group). Differences between IL-1-treated and control mice were significant ($\chi^2 = 10.34$; $P < 0.005$), whereas differences between ACTH-treated and vehicle-treated mice were not significant.

12 h after infection in all treatment groups (Fig. 3). The corticosterone concentrations in vehicle-treated and ACTH-treated mice did not differ significantly at any time point. In IL-1-treated mice, however, corticosterone levels were lower than those in the control mice (significantly different at 36 and 48 h) and the ACTH-treated group (significantly different at 12 and 36 h) (Fig. 3). Signs of discomfort of the infected animals (piloerection, decreased physical activity) were less pronounced in the IL-1-treated group.

DISCUSSION

In the present study we examined the role of glucocorticosteroids in IL-1-induced protection to a lethal bacterial challenge in mice. Preexposure to 800 ng of IL-1 24 h before a gram-negative bacterial challenge enhances survival in normal and neutropenic mice (24, 25). Administration of a low dose (800 ng) of rhIL-1 β to both normal or neutropenic mice resulted in an elevated plasma corticosterone level for 8 to 12 h; this is similar to what other investigators have found in nonneutropenic mice (5). Several investigators have studied the administration of glucocorticosteroids shortly

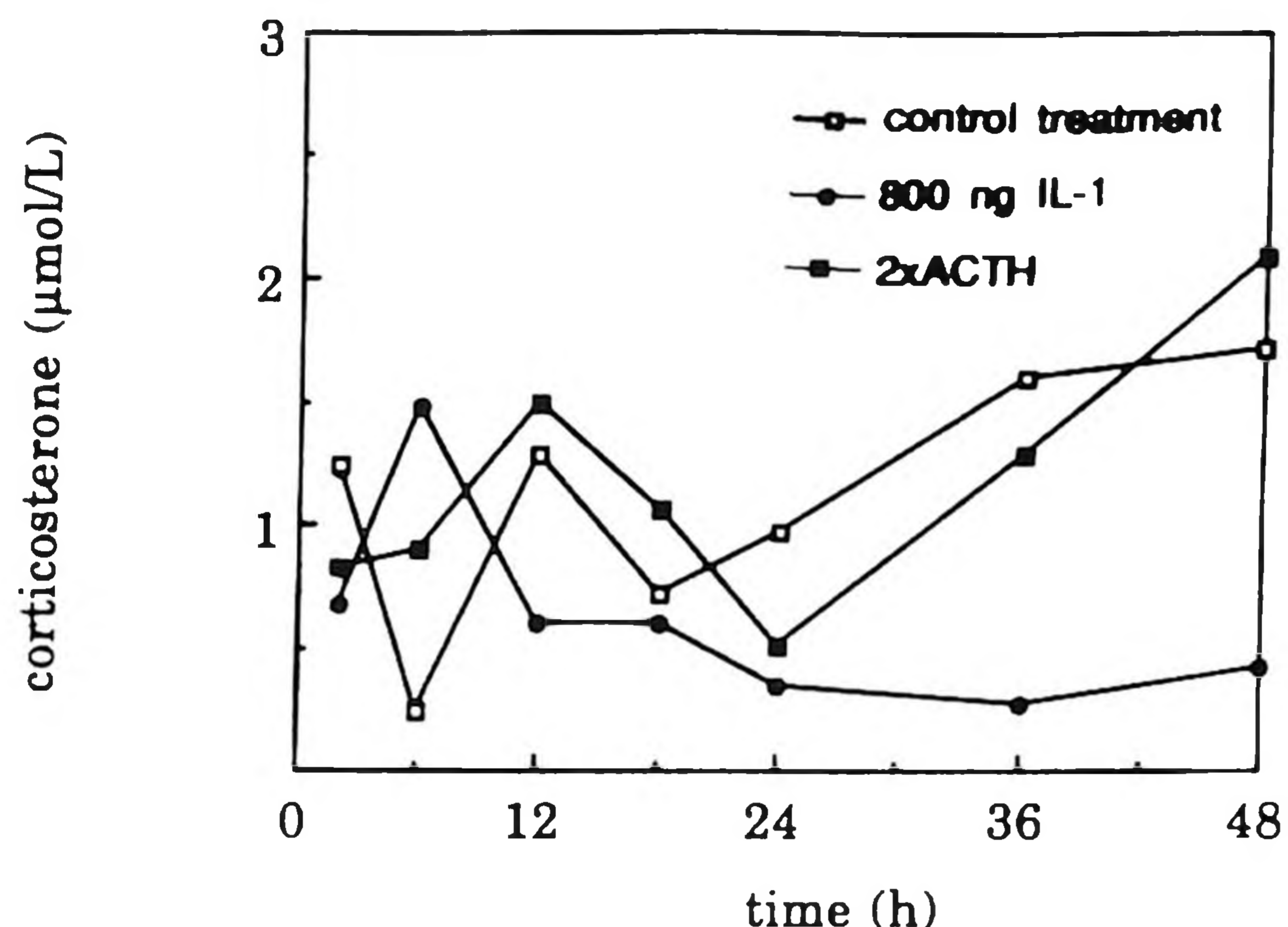


FIG. 3. Median corticosterone levels after i.m. infection at time zero of normal mice with *K. pneumoniae* 24 h after pretreatment with 800 ng of rhIL-1 β , two doses of 50 μ g of ACTH_[1-24], or control treatment (six mice per datum point). Corticosterone levels after IL-1 pretreatment were significantly lower than those in control treated mice at 36 and 48 h ($P = 0.03$ and $P = 0.02$, respectively) and than those in ACTH-treated mice at 12 and 36 h ($P = 0.04$ and $P = 0.009$, respectively). Differences between ACTH-treated and control groups were not significant.

before or after a challenge with endotoxin, microorganisms, or other noxious substances and found that they have a protective effect on survival (1, 8, 17). Although plasma corticosterone concentrations in our study peaked 20 h before the infectious challenge and returned to normal at the time of infection, a protective effect by the transiently increased level of corticosterone cannot be excluded a priori, since several effects of glucocorticosteroids are long-lasting or are delayed for many hours (2, 15, 19, 31). Also, our finding of a difference in corticosterone levels induced by a protective (800 ng) versus a nonprotective (80 ng) dose of IL-1 might be in accordance with a role of glucocorticosteroids in the protective effect of IL-1. However, when we mimicked the plasma corticosterone concentration curve induced by 800 ng of IL-1 by administration of synthetic human ACTH to both normal and neutropenic mice, no protection against lethal bacterial infection was found. This indicates that protection by IL-1 is not mediated by the elevated levels of glucocorticosteroids.

During infection, levels of glucocorticosteroids in plasma increase. The early presence of adequate concentrations of glucocorticosteroids is probably necessary for effective control of overshooting of the normal defense reactions that occurs during infection and injury (3, 15). Glucocorticosteroids suppress the production and the effects of many of the mediators that play a role in tissue injury in severe infections (7). Production of primary mediators, like the cytokines IL-1, tumor necrosis factor, IL-6, and gamma interferon, and secondary mediators is inhibited by glucocorticosteroids (6, 12, 15, 18, 23). In addition, glucocorticosteroids play a role in the induction of the secretion of acute-phase proteins, many of which possess anti-inflammatory and detoxifying effects (22). A physiological role of these hormones during infection is further supported by the increased sensitivity of adrenalectomized rodents to the toxic effects of endotoxin, inflammatory cytokines, and other inflammatory mediators, a sensitivity that can be reversed by administration of glucocorticosteroids (3, 4). In various studies of gram-

negative sepsis and endotoxin shock in animals, increased survival after high-dose glucocorticosteroid pretreatment has been documented (17, 21). Therefore, we also examined the impact of IL-1 pretreatment on the glucocorticoid response after an infectious challenge. Interestingly, we found lower corticosterone levels in IL-1-pretreated mice during infection. Since the IL-1-treated mice all survived the challenge, these relatively low corticosterone levels may reflect the better physical condition of these mice; the higher steroid levels in the vehicle- and ACTH-treated mice might be a consequence of the lethal illness.

In conclusion, the data presented here suggest that the increase in resistance to infection induced by IL-1 is not due to the effect of this cytokine on glucocorticosteroid production. The improved outcome of infection in animals treated with IL-1 is associated with lower plasma corticosterone levels during the course of infection.

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