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# Interleukin-1 (IL-1)-Induced Resistance to Bacterial Infection: Role of the Type I IL-1 Receptor

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**Pretreatment with a low dose of recombinant human interleukin-1 $\beta$  (IL-1) (3 to 30  $\mu$ g/kg) 24 h before a lethal *Pseudomonas aeruginosa* infection prolongs survival in neutropenic mice. We investigated the role of the type I IL-1 receptor (IL-1RI) and IL-1RII in this IL-1-induced protection by using a specific IL-1 receptor antagonist (IL-1Ra), which blocks effects mainly via IL-1RI. Pretreatment with IL-1Ra before IL-1 partially blocked the IL-1-induced enhanced survival, whereas pretreatment with a specific neutralizing monoclonal antibody to IL-1RI (35F5) eliminated the IL-1 induced protection. The nonapeptide fragment 163-171 of recombinant human IL-1 $\beta$ , which possesses the immunoadjuvant but not the inflammatory effect of the entire molecule via a non-receptor-mediated signal transduction process, did not reproduce the IL-1-induced protection. IL-1-induced protection was associated with reduced serum aspartate aminotransferase and alanine aminotransferase concentrations in conjunction with ameliorated histopathology of the liver. These findings may be due to reduced cytokine production and cytokine sensitivity of target cells after infection. We conclude that the IL-1-induced nonspecific resistance to infection is mediated by cells bearing IL-1RI and is associated with a reduction of liver damage.**

Administration of the proinflammatory cytokine interleukin-1 (IL-1) leads to enhanced nonspecific resistance to gram-positive and gram-negative bacteria, fungi, and plasmodia (27). For example, we have shown that pretreatment with a single low dose (3 to 30  $\mu$ g/kg) of recombinant human IL-1 $\beta$  (rhIL-1 $\beta$ ) 24 h before a lethal gram-negative infectious challenge with *Klebsiella pneumoniae* or *Pseudomonas aeruginosa* enhances the survival of normal and neutropenic mice, respectively (19, 20). The mechanism of this protection has been only partially clarified. A direct antimicrobial effect of IL-1 has been excluded in vitro (19), and whether IL-1 induces enhanced clearance of microorganisms in vivo is controversial (27). The protective effect of IL-1 against infectious challenges in granulocytopenic mice indicates that neutrophils do not play a major role (19, 27). Glucocorticosteroids, eicosanoids, or cytokines such as IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor are not likely to mediate the IL-1-induced resistance to infection (22-24, 26). However, IL-1-induced tumor necrosis factor alpha and IL-1-induced acute-phase proteins play some role as mediators of the IL-1 effect (22, 23).

Two receptors for IL-1, which differ in both size and tissue distribution, have been fully characterized (11, 16). The type I IL-1 receptor (IL-1RI) is an 80-kDa protein present on T lymphocytes, endothelial cells, fibroblasts, and hepatocytes, and IL-1RII is a 68-kDa protein found on B lymphocytes, monocytes, and neutrophils (5). In the present study, we have investigated the roles of IL-1RI and IL-1RII in the IL-1 $\beta$ -induced protection against infection in mice by using neutralizing monoclonal antibodies to murine IL-1RI and IL-1RII, respectively (5, 7). We also used the IL-1 receptor antagonist (IL-1Ra), a naturally occurring 25-kDa glycoprotein belonging to the IL-1 gene family, which blocks IL-1 effects by specifically

binding mainly to IL-1RI without agonist activity (1). To further elucidate the role of IL-1 receptors, we investigated whether the immunostimulatory 163-171 nonapeptide fragment of human IL-1 $\beta$ , which acts via a non-receptor-mediated signal transduction pathway (3, 4), exerts protective activity.

Recently, we demonstrated that the IL-1-induced protection against infection is associated with reduced concentrations of tumor necrosis factor alpha and IL-6 in plasma during infection together with an increased level of mRNA for the anti-inflammatory IL-1Ra (25). In the present study, we have also investigated whether this IL-1-induced modulation of cytokine responses is reflected in a decrease in liver damage.

## MATERIALS AND METHODS

**Mice.** Female outbred Swiss mice (weight, 20 to 25 g; TNO, Rijswijk, The Netherlands) were kept under specific-pathogen-free conditions. Standard irradiated lab chow (RMH-TM; Hope Farms, Woerden, The Netherlands) and acidified water were available ad libitum.

**Materials.** rhIL-1 $\beta$  was generously provided by P. Graber (Glaxo, Geneva, Switzerland). Human IL-1Ra (1) was donated by J. Vannice, Synergen, Boulder, Colo. Inactivated rhIL-1 $\beta$  and IL-1Ra (control treatments) were prepared by heating rhIL-1 $\beta$  and IL-1Ra at 95°C for 30 min. For in vivo administration, rhIL-1 $\beta$ , IL-1Ra, and the control proteins were dissolved in pyrogen-free phosphate-buffered saline (pH 7.4) with 2% (vol/vol) mouse serum.

35F5, a rat immunoglobulin G1 (IgG1) anti-mouse IL-1RI monoclonal antibody (5), was a kind gift from R. Chizzonite, Hoffmann-La Roche, Nutley, N.J. As a control antibody, a purified rat IgG (I-4131) was obtained from Sigma Immunochemicals (St. Louis, Mo.). ALVA-42, a murine IgG1 monoclonal antibody blocking the murine IL-1RII (7), and the IL-1 $\beta$  peptide 163-171 (4) were donated by P. Ghiara (Sclavo, Siena, Italy). Purified mouse IgG (I-5381), used as control antibody for ALVA-42, was obtained from Sigma.

**Survival experiments.** Since *P. aeruginosa* (ATCC 27853) does not kill normal mice, mice were rendered neutropenic ( $<0.5 \times 10^9$  granulocytes per liter) by two subcutaneous injections of cyclophosphamide (ASTA Pharma, Frankfurt, Germany) on days 4 and 1 before challenge (150 and 100 mg/kg, respectively). On day 1 before challenge, 800 ng of human IL-1 $\beta$  or control treatment was injected intraperitoneally (i.p.) in 0.1 ml; 24 h later (time zero), a lethal challenge with  $0.5 \times 10^7$  to  $1 \times 10^7$  CFU of *P. aeruginosa* was given intramuscularly in the left thigh muscle. Six hours after the infection, gentamicin (120 mg/kg; Schering, Kenilworth, N.J.) was administered subcutaneously in order to postpone the time of death and thus accentuate the differences between treatment groups. Mortality was recorded for at least 48 h.

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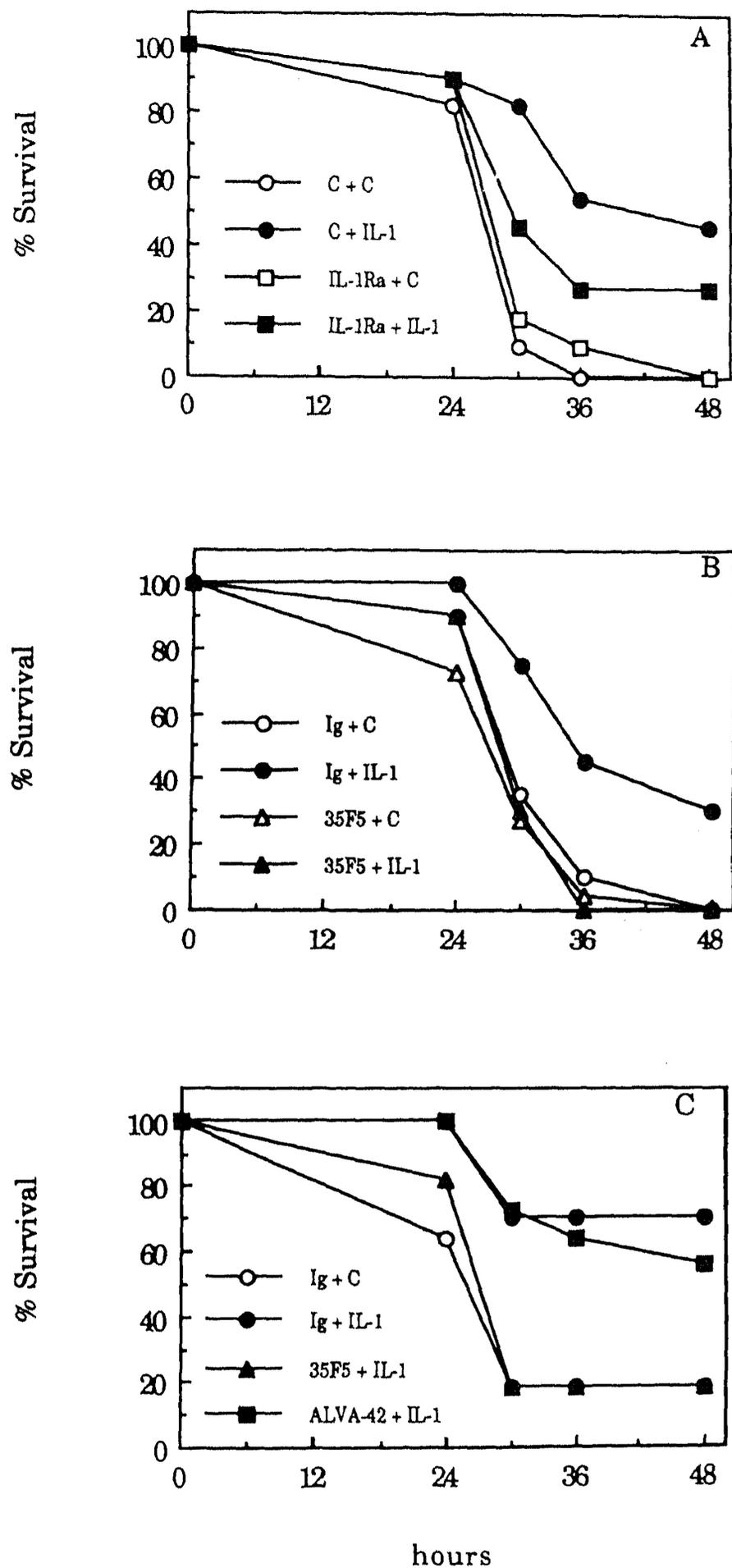


FIG. 1. Survival of neutropenic mice infected intramuscularly with *P. aeruginosa* (time zero) after various pretreatments. (A) Mice were pretreated at 24.25 h before infection with 800  $\mu$ g of IL-1Ra or inactivated IL-1Ra (control treatment [C]) i.p. and at 24 h before infection with 800 ng of rhIL-1 $\beta$  or inactivated IL-1 $\beta$  (control treatment) i.p. Mice pretreated with inactivated IL-1Ra and 800 ng of IL-1 were protected significantly in comparison to mice receiving control injections on both occasions ( $\chi^2 = 9.79$ ;  $P < 0.005$ ), whereas mice pretreated with 800 ng of IL-1Ra followed by 800 ng of IL-1 were protected to a nonsignificant extent. The difference between IL-1-treated mice pretreated with IL-1Ra and those pretreated with inactivated IL-1Ra was not significant. Also, the difference between mice receiving either IL-1Ra or inactivated IL-1Ra followed by inactivated IL-1 was not significant (22 mice per group). (B) Mice were pretreated i.p. at 42 h before infection with 200  $\mu$ g of the neutralizing anti-IL-1RI antibody 35F5 or control IgG and at 24 h before infection with 800 ng of rhIL-1 $\beta$  or inactivated rhIL-1 $\beta$  (control treatment) i.p. Mice receiving control IgG followed by IL-1 were protected significantly in comparison to mice receiving control IgG followed by inactivated IL-1 ( $\chi^2 = 6.13$ ;  $P < 0.025$ ). The survival of IL-1-treated mice pretreated with 35F5 was not significantly different from that of control treated mice pretreated with 35F5. Also, the difference between

**Liver enzymes.** For assessment of the effect of IL-1 on liver enzymes, aspartate aminotransferase (ASAT) levels and alanine aminotransferase (ALAT) levels in nonhemolytic EDTA-plasma from IL-1-pretreated and control neutropenic mice were measured 24 h after intramuscular *P. aeruginosa* infection. ASAT and ALAT levels were assessed by routine procedures (BM/Hitachi 747; Boehringer Mannheim, Mannheim, Germany).

**Statistical analysis.** Survival data were analyzed by use of the log rank test (14). Comparisons of biochemical and histopathologic data between treatment groups were made by the Kruskal-Wallis test.  $P$  values of less than 0.05 were considered significant.

## RESULTS

**Effect of IL-1Ra and IL-1RI and IL-1RII antibodies on IL-1-induced protection against infection.** To investigate the involvement of IL-1RI and IL-1RII in the IL-1-induced enhanced resistance to infection, IL-1Ra, which inhibits IL-1 effects mainly via IL-1RI (10), was administered in a 100 to 1,000-fold molar excess over IL-1. Doses of IL-1Ra varying from 40 to 250  $\mu$ g administered i.p. 15 min before 800 ng of IL-1 i.p., analogous to the regimen found to be effective by others (10), did not significantly reduce the IL-1-induced protection of neutropenic mice against a lethal *P. aeruginosa* challenge (not shown). After 800  $\mu$ g of IL-1Ra, a 1,000-fold molar excess over IL-1, there was a trend to reduction of the IL-1-induced protection, although the difference between the IL-1-treated group given a control pretreatment and that given IL-1Ra pretreatment did not reach significance (Fig. 1A). These results suggest a potential role for IL-1RI in the IL-1-induced protection against infection. IL-1Ra, however, is not completely specific for IL-1RI, since it also binds to the murine IL-1RII, albeit with a much lower affinity (10, 11). Therefore, complete inhibition of the IL-1 effect by using even higher doses of IL-1Ra would not allow one to distinguish between a complete effect via IL-1RI due to more effective blockade and an additional IL-1 effect via IL-1RII.

In an alternative approach to establish the possible role of IL-1RI or IL-1RII, we performed experiments with 35F5, a specific neutralizing rat anti-murine IL-1RI monoclonal antibody (5), and ALVA-42, a monoclonal antibody directed against the murine IL-1RII (2, 7).

Pretreatment with 35F5 (200  $\mu$ g i.p.), 4 h before IL-1, was almost fully effective, reducing significantly the IL-1-induced enhanced survival ( $\chi^2 = 5.92$ ;  $P < 0.025$ ) to nonsignificant protection ( $\chi^2 = 2.53$ ;  $P = 0.12$ ) (12 mice per group) (data not shown). When the same i.p. dose of 35F5 was administered 18 h before IL-1, it abrogated the IL-1-induced protection, corroborating the data obtained with IL-1Ra (Fig. 1B). Survival after pretreatment of control-treated infected mice with 200  $\mu$ g of either rat IgG or 35F5 did not differ significantly from survival after pretreatment with saline, and therefore only results for the saline-pretreated group are presented in Fig. 1B.

When pretreatment with either 35F5 or ALVA-42 was performed within one experiment, the complete inhibition of the IL-1 effect by 200  $\mu$ g of 35F5 administered 18 h before IL-1

mice receiving either control IgG or 35F5 followed by inactivated IL-1 was not significant (20 mice per group). (C) Mice were pretreated i.p. at 42 h before infection with 200  $\mu$ g of 35F5, ALVA-42, or control IgG and at 24 h before infection with 800 ng of rhIL-1 $\beta$  or inactivated rhIL-1 $\beta$  (control treatment) i.p. Mice receiving IgG followed by IL-1 were protected significantly in comparison to mice receiving IgG followed by inactivated IL-1 ( $\chi^2 = 6.63$ ;  $P = 0.01$ ). Mice receiving ALVA-42 followed by IL-1 were protected significantly in comparison to mice receiving ALVA-42 followed by inactivated IL-1 ( $\chi^2 = 3.86$ ;  $P = 0.05$ ). The difference in survival between IL-1-treated mice pretreated with ALVA-42 and those pretreated with control IgG was not significant. The survival of IL-1-treated mice pretreated with 35F5 did not differ significantly from that of mice pretreated with inactivated IL-1 and pretreated with either 35F5 or control IgG (10 or 11 mice per group).

was confirmed, whereas no effect was observed with 200  $\mu\text{g}$  of ALVA-42, a dose reported to be effective in reduction of lipopolysaccharide lethality (2, 7) (Fig. 1C). The survival of mice that received heat-inactivated IL-1 and pretreatment with either rat IgG, 35F5, or ALVA-42 did not differ from that of mice treated with inactivated IL-1 and pretreated with murine IgG; therefore, in Fig. 1C only results for the latter group are shown. Since the survival of IL-1-treated mice pretreated with rat IgG did not differ significantly from that of mice pretreated with murine IgG, only results for the latter group are presented.

**Effect of 163-171 peptide pretreatment on survival after infection.** Next, we investigated the effect of the nonapeptide fragment (163-171) of human IL-1 $\beta$ , which lacks a series of the inflammatory and acute-phase effects of the entire molecule but possesses a range of immunostimulating effects via non-IL-1R-mediated pathways (3, 4).

Whereas significant protection was produced by i.p. injection of 800 ng of IL-1 into neutropenic mice 24 h before a lethal *P. aeruginosa* infection, i.p. pretreatment with nonapeptide doses varying from 1 to 320  $\mu\text{g}$  (a 21- to 6,800-fold molar excess over IL-1), which have been found to be effective by others (3, 18), did not enhance survival (not shown). Combined i.p. administration of the same doses of the nonapeptide and 800 ng of IL-1 did not affect the IL-1-induced protection against infection (not shown).

**Effect of IL-1 pretreatment on liver enzymes after infection.** For assessment of liver injury in infected mice, ASAT and ALAT levels in blood obtained from IL-1-pretreated and control-treated neutropenic mice were determined 24 h after a lethal intramuscular *P. aeruginosa* challenge, a time point at which no mice had yet succumbed. ALAT concentrations were significantly reduced in the IL-1-pretreated group compared with the control group (101 and 367 U/liter, respectively;  $P = 0.0095$ ), whereas ASAT concentrations were not significantly reduced (819 and 1,340 U/liter, respectively) (seven to nine mice per group).

## DISCUSSION

In this study, we found that IL-1RI and not IL-1RII mediates the protective effect of rhIL-1 $\beta$  in lethal *P. aeruginosa* infection in neutropenic mice.

The role of IL-1RI was first investigated by using IL-1Ra, a competitive inhibitor of IL-1 $\alpha$  and IL-1 $\beta$  binding mainly to IL-1RI (1). A 1,000-fold molar excess of IL-1Ra over IL-1 partially blocked the IL-1-induced protection. Since high doses of IL-1Ra may also block IL-1 effects via IL-1RII (1, 10), which has much less affinity for IL-1Ra, studies with higher doses of IL-1Ra would not differentiate between a more effective blockade of IL-1 effects via IL-1RI or a partial effect of IL-1 via IL-1RII. Therefore, we used 35F5, a specific neutralizing antibody directed against the murine IL-1RI (5). Pretreatment with 35F5 eliminated the IL-1-induced protection against infection, suggesting that this IL-1 effect is mediated via cells bearing IL-1RI. The complete lack of reduction of the IL-1-induced enhanced survival by pretreatment with ALVA-42, which is reported to block IL-1RII (2, 7), underscores the role of IL-1RI. However, a recent report (6) suggests that this antibody does not bind to IL-1RII, which may be another explanation of the lack of effect. Neta et al. (12) also found that radioprotection induced by IL-1 pretreatment could be blocked by the 35F5 antibody, suggesting that IL-1RI was mediating this response. The key role of IL-1RI is corroborated by the recent paper of Sims et al. (17) reporting that the IL-1-induced signal transduction is mediated exclusively via

this receptor. Which type of IL-1RI-bearing cells play a role in the IL-1-induced protection remains to be clarified. Our previous report (22) on a role of acute-phase proteins, produced by hepatocytes, which bear IL-1RI (10), is in accordance with the findings of this study. The same holds for induction by IL-1 of tumor necrosis factor alpha, which may be produced by endothelial cells, by fibroblasts, and by monocytes via small quantities of IL-1RI (17), and which has been shown in our protection studies to play some role (23). It is of interest that neither IL-1Ra nor 35F5 alone was able to affect survival, as has been found in other studies (10). However, this may largely be explained by the single administration and the short half-lives of these reagents.

The IL-1-induced enhanced survival after infection could not be mimicked by the nonapeptide fragment (161-173) of rhIL-1 $\beta$ . This immunostimulatory domain of rhIL-1 $\beta$  lacks inflammatory effects such as pyrogenicity and induction of prostaglandins, IL-6, glucocorticosteroids, and acute-phase proteins (4). Boraschi et al. recently reported that the nonapeptide enters the cell through a receptor-independent mechanism, possibly by passive diffusion through the cell membrane (3). This would be in accordance with the role of the IL-1RI-mediated signal transduction pathway of the IL-1 effect in our studies.

The finding of lower concentrations of ASAT and ALAT, markers of hepatocyte necrosis, in sera of IL-1-pretreated mice after infection is in accordance with our previous finding of IL-1-induced amelioration of liver histopathology (i.e., less glycogen depletion, fatty degeneration, and cell necrosis) (21, 21a). Such protection is reminiscent of the IL-1-induced protection against acetaminophen-induced hepatotoxicity (15).

The exact mechanism of the IL-1-induced protection of liver hepatocytes and cells in other organs remains to be elucidated. An excess of cytokines and more distal inflammatory mediators such as leukotrienes, platelet-activating factor, nitric oxide, and superoxide radicals produced during lethal infection may be responsible for many pathologic phenomena. Recently, we were able to show that IL-1 pretreatment reduces cytokine production (25), and a role of this mechanism in the ameliorated pathologic changes is likely. On the other hand, antagonists of leukotrienes, prostaglandins, and platelet-activating factor were found not to affect IL-1-induced protection (23). In addition, IL-1 pretreatment might induce protection via desensitization of the host to the overshoot of cytokines and inflammatory mediators (28). Such desensitization may occur either by induction of protective substances such as acute-phase proteins, soluble cytokine receptors, or receptor antagonists (9, 22, 28), by downregulation of cytokine receptors, or by induction of intracellular protective proteins such as Mn-superoxide dismutase, heat shock proteins, or other protective proteins in target cells (8, 13).

In conclusion, the IL-1-induced protection against *P. aeruginosa* infection in neutropenic mice seems to be mediated via IL-1RI. The nonapeptide fragment of rhIL-1 $\beta$  is not protective. The IL-1-induced protection is associated with a significant reduction in biochemical signs of hepatocyte damage, possibly reflecting the IL-1-induced reduction of cytokine overshoot during infection.

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