Contribution of Interleukin-1 to Activation of Coagulation and Fibrinolysis, Neutrophil Degranulation, and the Release of Secretory-Type Phospholipase A2 in Sepsis: Studies in Nonhuman Primates After Interleukin-1α Administration and During Lethal Bacteremia


Although studies with interleukin-1 receptor antagonist (IL-1ra) in animal models have shown that IL-1 contributes to mortality in sepsis, the mechanisms whereby IL-1 mediates lethal effects are not well established. A possible mechanism is that IL-1 enhances the activation and release of other inflammatory mediator systems such as coagulation, fibrinolysis, neutrophils, and secretory-type phospholipase A2 (sPLA2). We investigated this possibility by assessing the effect of intravenously injected recombinant human IL-1α (rhlL-1α) on these plasma parameters in baboons. In addition, we examined the course of these inflammatory parameters in baboons after a challenge with a lethal dose of Escherichia coli while receiving a 24-hour constant infusion of IL-1ra or placebo. Intravenous administration of IL-1α (10 μg/kg) induced the formation of thrombin, as evidenced by the appearance of thrombin-antithrombin III (TAT) complexes in the circulation (peak levels, 188 ± 92 ng/mL at 2 hours), as well as the activation of fibrinogen, assessed by circulating plasmin-α2-antiplasmin complexes (PAP complexes; peak levels, 0.4% ± 0.03% of fully activated plasma at 1 hour), the release of tissue-type plasminogen activator (t-PA; peak levels, 6 ± 2 ng/mL at 2 hours), and its inhibitor, plasminogen activator inhibitor (PAI; peak levels, 724 ± 246 ng/mL at 4 hours). IL-1α administration also induced the release of sPLA2 (maximal levels, 336 ± 185 ng/mL at 8 hours), but not degranulation of neutrophils. In the septic baboons, a significant reduction of the formation of thrombin (peak TAT levels decreased from 582 ± 78 ng/mL to 219 ± 106 ng/mL; P < .005), the release of t-PA (peak levels decreased from 71 ± 11 ng/mL to 17 ± 2 ng/mL; P < .001), and its inhibitor, PAI (peak levels decreased from 2,639 ± 974 ng/mL to 1,110 ± 153 ng/mL; P < .001), was observed in the group receiving IL-1ra compared with that receiving placebo. The release of neutrophil elastase was also significantly attenuated in IL-1ra-treated animals (peak levels, 1,024 ± 393 and 655 ± 104 ng/mL in control and treatment groups, respectively; P < .05). The difference between sPLA2 levels in both septic groups, although higher in the controls (maximal levels, 3,140 ± 1,435 ng/mL in control vs. 2,217 ± 1,375 ng/mL in IL-1ra-treated group), was not significant. Thus, IL-1 contributes to activation of various other mediator systems in severe sepsis in nonhuman primates. We propose that these effects may explain the lethal actions of IL-1 in this sepsis model and suggest a similar role for IL-1 in severe human sepsis.

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INTERLEUKIN-1 (IL-1) is a pleiotropic proinflammatory cytokine that is considered to play a proximal role in the initiation and regulation of the inflammatory cascade ensuing in response to endotoxins or bacteremia.1-4 This inflammatory cascade includes the release or formation of mediators such as cytokines, oxygen radicals, and eicosanoids, as well as the activation of coagulation and fibrinolytic systems and degranulation of neutrophils.5,6 In vitro studies have indicated that IL-1 is able to induce the release or activation of a number of these mediators.1,5,6,7 For example, IL-1 is capable of inducing the release of other cytokines such as IL-6 and IL-8, stimulating the expression of procoagulant activity on cultured human endothelial cells, and inducing the formation of eicosanoids in macrophages and endothelial cells.5,6-10 However, knowledge of the in vivo effects of IL-1 is limited, although its ability to induce the release of IL-6 and IL-8 has been reported.11,12

Studies with a specific antagonist of IL-1 receptors, IL-1 receptor antagonist (IL-1ra), in animal models have clearly indicated an essential role of IL-1 in the lethal complications of sepsis, as pretreatment with IL-1ra afforded significant protection in animals challenged with a lethal dose of bacteria or endotoxin.1,2,13,14 How IL-1 contributes to mortality in these conditions is not well known. In this study, we investigated the possibility that the lethal effects of IL-1 in sepsis are due to its effects on the activation and release of other inflammatory mediator systems. Therefore, we established in a primate model the effect of intravenous administration of IL-1α on a number of plasma parameters that reflect activation of coagulation and fibrinolysis, degranulation of neutrophils, and formation of phospholipase A2 (PLA2). In addition, we analyzed the course of these parameters in baboons challenged with a lethal dose of Escherichia coli while receiving IL-1ra or placebo (a model previously described...

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by Fischer et al. Our results indicate that IL-1 contributes to the activation and release of other inflammatory mediator systems in sepsis.

**MATERIALS AND METHODS**

**Reagents**

Recombinant human IL-1α (rhIL-1α) was provided by Hoffmann-La Roche, Inc (Nutley, NJ). Recombinant human IL-1ra was produced by Synergen, Inc (Boulder, CO). To obtain an appropriate concentration, both reagents were diluted in saline (0.9%, wt/vol, sodium chloride) before intravenous administration.

**IL-1α Administration to Baboons**

A detailed report of the study protocol as well as the hemodynamic, metabolic, and hormonal responses after IL-1α administration to baboons has been published previously. Notably, the quantities peak levels of IL-1α previously reported during lethal bacteremia with ketamine hydrochloride (10 mg intramuscularly [IM]). During the duration of the study, anesthesia was maintained using sodium pentobarbital (5 mg/kg intravenously [IV]). The animals were randomly assigned to treatment or control group. All animals received a bolus intravenous injection of IL-1ra, 25 μg/kg/min, for 24 hours. Animals in the control group received a bolus intravenous injection of IL-1ra, 10 μg/kg/min, for 24 hours and were resuscitated with saline, 10 mL/kg, every 15 minutes whenever they met the criteria described by Fischer et al. From 8 to 24 hours, fluid resuscitation was abolished, and the animals only received a continuous infusion of saline of 1 mL/kg/h containing either IL-1ra or placebo. After 24 hours, all surviving animals were killed according to Institutional Animal Care and Use Committee guidelines. The course of the septic process and the hemodynamic, metabolic, and cytokine responses in IL-1ra— and placebo—treated baboons have been described in detail elsewhere. These data were reported for 14 animals (seven animals receiving IL-1ra and seven animals receiving placebo), whereas for the present study, plasma samples of six animals receiving IL-1ra (treatment group) and five animals receiving placebo (control group) were available for measurements of inflammatory mediator systems.

Heparinized arterial blood samples were obtained from the animals before E coli administration (t = 0) and at regular intervals thereafter. Plasma was obtained by centrifugation at 4°C and stored at −70°C until assayed. For the present study, samples obtained during the first 12 hours were analyzed.

**Assays**

Thrombin-antithrombin III (TAT) complexes were measured with an enzyme-linked immunosorbent assay (ELISA) as described elsewhere. Briefly, a purified monoclonal antibody (MoAb) raised against human (pro)thrombin (CLB-TR3) was used as a capture antibody, and biotinylated MoAb CLB-ATIII-0 against antithrombin III in combination with streptavidin-polymerized horseradish peroxidase was used to detect bound complexes. Results of baboon plasma were expressed as nanograms per milliliter by reference to dilutions of an in-house standard, pooled normal human serum, which was equilibrated to purified human TAT complexes. The lower limit of detection of this assay is 1 ng/mL.

Tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) concentrations were determined using ELISAs as previously described. Values were expressed as nanograms per milliliter. The lower limits of detection are 1 and 5 ng/mL, respectively.

Plasmin-α1-antiplasmin (PAP) complexes were measured with a radioimmunoassay (RIA) as described. Levels of PAP complexes were expressed as percentage of the level present in normal baboon plasma, in which a maximal amount of complexes was generated by incubation with an equal volume of urokinase (50 μg/mL) in the presence of 0.4 mol/L methyamine to inactivate α1-macroglobulin, further referred to as NBP-MA-UK. The lower limit of detection of this assay is 0.01% of NBP-MA-UK.

Elastase-α1-antitrypsin complexes were assessed with a RIA that has been described in detail elsewhere. Results were expressed as nanograms of elastase complexes per milliliter by reference to a standard curve consisting of normal baboon plasma to which human neutrophil elastase (Elastin Products Co, Pacific, MO) was added at a final concentration of 2 μg/mL. In this standard, more than 95% of the elastase is complexed to α1-antitrypsin. The lower limit of detection is 25 ng/mL; normal values are less than 100 ng/mL.

**PLA2 concentrations in baboon plasma** were determined with an ELISA that was modified from that reported by Smith et al. MoAbs against human secretory PLA2 type II (provided by Dr F.B. Taylor Jr, Oklahoma Medical Research Foundation, Oklahoma City, OK) were used as the coating and catching antibodies, respectively. Results are expressed by reference to a standard curve consisting of a dilution of culture supernatant of HepG2 cells stimulated with IL-8, in which the amount of PLA2 was assessed by comparison with recombinant human secretory-type PLA2 (sPLA2; courtesy of Prof H.M. Verheij, Department of Enzymology and Protein Engineering, University of Utrecht, Utrecht, The Netherlands). The lower limit of detection of this assay is 2.5 ng/mL.

**Statistical Analysis**

Values are expressed as means ± SEM. Statistical analysis was performed using a commercial statistical package (StatView; Abacus Concepts, Inc, Berkeley, CA). Comparisons between groups during the course of the observation period were performed using repeated measures analysis of variance (ANOVA). Within one group, differences from baseline levels were assessed with ANOVA using Fisher’s least significant difference (Fisher PLSD). Statistical significance was designated at the 95% confidence level.

**RESULTS**

**Effect of IL-1α Infusion in Baboons**

General. As reported previously, 10 μg/kg of IL-1α did not lead to lethal effects. However, clear hemodynamic, metabolic, and cytokine responses were observed.
metabolic, and hormonal changes were found, as well as a significant increase in IL-6 levels without measurable levels of tumor necrosis factor (TNF).

**Coagulation response.** To investigate whether IL-1α is capable of inducing a coagulation response, we measured circulating TAT complexes after infusion of 10 μg/kg IL-1α in baboons. As is shown in Fig 1, after IL-1α administration, TAT levels gradually increased to a maximum at 2 hours that was significantly different from baseline values (t = 0 v t = 2 hours, P < .05, Fischer PLSD), after which levels declined but were still elevated at 8 hours after the start of the infusion.

**Fibrinolytic response.** IL-1α administration induced a significant fibrinolytic response (Fig 2A through C). A significant and transient increase of PAP levels, which reflects the generation of plasmin, the key enzyme of the fibrinolytic system, occurred 1 hour after the infusion of IL-1α, leading to maximum values of 0.4% ± 0.03% (P < .05, Fischer PLSD; Fig 2A). Levels of t-PA were significantly elevated from baseline at 1 hour and thereafter (P < .05, Fischer PLSD), with peak levels of 6 ± 2 ng/mL (Fig 2B). The course of PAI is shown in Fig 2C. After administration of IL-1α, PAI levels were significantly elevated from baseline at t = 2.5 hours and thereafter (P < .05, Fischer PLSD), reaching a plateau with a maximal level of 724 ± 246 ng/mL at 4 hours.

**Neutrophil degranulation.** Administration of IL-1α was not followed by a significant release of elastase from neutrophils. Over the 8-hour study period, circulating elastase-α1-antitrypsin complexes remained below 100 ng/mL in all animals, and no significant increase from baseline levels was observed (data not shown).

**Plasma levels of PLA2.** Formation of sPLA2 was induced by the infusion of IL-1α, although a significant increase was not observed until 8 hours after the infusion (Fig 3). At this time point, levels of 336 ± 185 ng/mL were detected (P < .05, Fischer PLSD).

**Effect of IL-1 Receptor Blockade in Lethal Bacteremia**

**Mortality rate.** As reported previously, within the first 24 hours after the E coli challenge, a 57% mortality rate was observed in the control group despite fluid resuscitation, whereas all animals of the treatment group survived this period. Among the baboons of the control group that we analyzed in the present study, there were three animals that died within 24 hours and two animals that were likely to have been long-term survivors (60% mortality).

**Activation pattern of coagulation.** Plasma levels of TAT complexes were measured to assess activation of coagulation in placebo- and IL-1α-treated animals. In the control group, administration of a lethal dose of E coli resulted in a profound coagulation response. TAT complexes started to increase at 1 hour, reaching peak levels of 582 ± 78 ng/mL 6 hours after the start of the E coli infusion. Thereafter, TAT complexes declined, resulting in levels of 180 ± 40 ng/mL at 12 hours (Fig 4). In contrast, in the treatment group, the increase of circulating TAT complexes was less pronounced, and a zenith of 219 ± 106 ng/mL was observed at 8 hours. The difference between the course of TAT levels in the two groups was significant (P < .005).
Activation pattern of fibrinolysis. Administration of E coli elicited a pronounced activation of the fibrinolytic system (Fig 5A through C). The appearance of PAP complexes in the circulation after the challenge with a lethal dose of E coli was not affected by IL-1ra treatment: in both groups, a transient but comparable increase in circulating PAP complexes occurred between 1 and 2 hours after the start of the E coli infusion, reaching peak levels of 2.4% ± 0.6% and 2.4% ± 2.0% of the standard in placebo- and IL-1ra–treated animals, respectively (Fig 5A). However, IL-1ra significantly abrogated the appearance of PAI and t-PA in the circulation (both, P = .0001; Fig 5B and C). In the control animals, PAI reached peak concentrations after 6 hours (2.639 ± 974 ng/mL) and t-PA, after 10 hours (37 ± 11 ng/mL). Peak concentrations of PAI and t-PA in animals infused with IL-1ra were significantly less, ie, 1,110 ± 153 ng/mL and 17 ± 2 ng/mL, respectively (Fig 5B and C).

Neutrophil degranulation. Plasma levels of elastase-α1–antitrypsin were measured to study the effect of IL-1 receptor blockade on neutrophil activation after lethal E coli challenge. Figure 6 shows that the E coli infusion was associated with an increase in elastase-α1–antitrypsin complexes. In the control group, elastase complexes sharply increased from t = 4 hours, reaching a zenith of 1,024 ± 393 ng/mL at 6 hours. This increase was less pronounced in the treatment group, in which peak levels of 655 ± 104 ng/mL at 8 hours were observed. The difference between the course of levels during the observation period was statistically significant (P = .01).

Plasma levels of sPLA₂. Levels of sPLA₂ were measured to estimate the formation of proinflammatory lipid mediators, ie, metabolic products of arachidonic acid. In both groups, steadily increasing levels of sPLA₂ were observed at t = 3 hours and thereafter (Fig 7). In the treatment group,
levels gradually decreased after having reached a maximum of 2,217 ± 1,375 ng/mL at 8 hours, whereas in the control group, levels continued to increase during the entire observation period, reaching levels of 3,140 ± 1,435 ng/mL at t = 12 hours. However, this difference in the course of circulating sPLA₂ between the two groups was not statistically significant.

DISCUSSION

The aim of this study was to establish a possible contribution of IL-1 to the activation of coagulation and fibrinolysis, the degranulation of neutrophils, and the release of PLA₂ in a model for E coli bacteremia and shock in nonhuman primates. This was achieved by evaluating the effect of administration of IL-1α to healthy baboons on activation or release of these inflammatory parameters, as well as by comparing the course of these parameters during lethal sepsis in animals that either received or did not receive IL-1ra treatment. It should be noted that although IL-1α was administered to a limited number of baboons, all three animals displayed a uniform response for the parameters described here, and the results presented are consistent with recent studies in cancer patients to whom IL-1β was administered. The results led us to conclude that IL-1 contributes to activation of coagulation and fibrinolytic systems, the degranulation of neutrophils, and, possibly, the release of sPLA₂ in this model for sepsis in nonhuman primates.

A lethal or sublethal dose of E coli is a potent stimulus for the generation of thrombin in baboons, as we also observed (Fig 4). In vitro studies have indicated that IL-1, similarly to TNF, can activate the coagulation pathway by inducing the expression of tissue factor and downregulation of thrombomodulin on endothelial cells. This effect of IL-1 was substantiated by the observation that IL-1α administration elicited the formation of TAT complexes and, hence, activation of coagulation (Fig 1). IL-1 endogenously produced during septic shock presumably exerts similar effects, as the generation of circulating TAT complexes was significantly attenuated in baboons that received continuous infusion of IL-1ra after a lethal E coli challenge (Fig 4). In a previous study, we have shown that IL-1 receptor blockade in lethal hypotensive bacteremia in baboons did not attenuate TNFα levels. Although TNFα can induce activation of coagulation in vitro and in vivo, a recent study of low-grade endotoxemia in chimpanzees has shown that administration of anti-TNF MoAb was unable to prevent the appearance of TAT complexes. However, this observation does not exclude the possibility that in the more severe model of sepsis used in the present study the observed increase of TAT complexes (Fig 4) in the septic animals receiving IL-1ra, although considerably less than in the nontreated animals, resulted from the direct action of TNF (and/or lipopolysaccharide).

Administration of IL-1α induced the release of t-PA and PAI (Fig 2B and C). Moreover, IL-1 receptor blockade in the septic baboons was associated with a significant reduction of these parameters (Fig 5B and C). These findings suggested that IL-1 or mediators produced in response to IL-1 may be involved in releasing t-PA and PAI from the endothelium in the septic baboons. To our surprise, we found no difference in levels of PAP complexes between treatment and control groups, whereas we did find an increase of these complexes after infusion with IL-1α (Fig 2A). Presumably, this is due to the fact that the blockade of IL-1 receptors obviously will have no effect until IL-1 appears in the circulation, ie, after 2 hours. At this time, the formation of PAP complexes, which reaches its maximum after 2 to 1.5 hours after the E coli challenge, is already inhibited by increasing PAI concentrations, thereby masking the subsequent effects of IL-1 blockade that would become effective only after 1.5 to 2 hours. As PAP concentration peaks before IL-1 reaches its peak, it may be that IL-1 facilitation of t-PA release is of secondary importance in this LD₁₀₀₀ E coli model; hence, the failure of IL-1ra to attenuate the generation of PAP complexes. Consistent herewith, t-PA levels were not affected until after 2 hours (Fig 5B), ie, at the time that IL-1 is appearing in the circulation. Interestingly, the in vivo effects of IL-1 on the release of t-PA are in contrast with in vitro
observations that IL-1 inhibits rather than stimulates the release of t-PA by endothelial cells. The reason for this discrepancy is not clear, although we speculate that it may be related to the potency of IL-1 (and TNF) to induce vasopressin, which in turn causes t-PA to be released by the endothelium.

The systemic release of neutrophil activation products has been associated with a poor outcome in patients with sepsis. In vitro studies have shown that TNF, IL-6, and IL-8 can induce neutrophil degranulation. Consistent with these data, an intravenous injection of TNF in humans elicits a rapid neutropenia followed by granulocyte degranulation, as reflected by the appearance of elastase-α,-antitrypsin complexes in the circulation. However, during experimental endotoxemia, anti-TNF MoAbs only partially inhibit the release of elastase, indicating that other agonists of neutrophil activation are also involved in this condition. As TNF and IL-1 have overlapping biologic effects, a potential role for IL-1 in neutrophil degranulation can be postulated, although contradictory findings have been published regarding this issue.

In our study, administration of IL-1ra significantly reduced circulating levels of elastase-α,-antitrypsin complexes, whereas IL-1ra infusion alone was unable to elicit the appearance of these complexes. This latter finding is consistent with a recent study performed by Ogilvie et al who were unable to detect neutrophil degranulation products in cancer patients to whom a low dose of IL-1β had been administered. Thus, our observations argue against a potent agonistic effect of endogenous IL-1 on neutrophils. Rather, these data imply that in this model of lethal sepsis, IL-1 might potentiate neutrophil activation by other agonists such as TNF, IL-8, and C5a. In agreement herewith are in vitro studies showing that IL-1, although not being able to degranulate neutrophils or to stimulate the oxidative burst, is capable of priming these cells, although this has been recently disputed by Elbim et al. Alternatively, Abe et al. presented evidence that IL-1 may be primarily involved in emigration of neutrophils through chemotactic actions or acting on endothelial cells, whereas TNF in turn activates extravasated neutrophils. Evidence for possible synergistic actions of TNF and IL-1 on neutrophils is supported by our findings that IL-1ra is not able to induce the release of either TNF or elastase.

A bolus injection of IL-1ra resulted in the release of sPLA2, while IL-1ra administration did not reduce levels of sPLA2 during lethal E coli bacteremia. Phospholipases A2 are enzymes that release arachidonic acid from membrane phospholipids, which is the rate-limiting step in the generation of thromboxane A2, prostaglandins, and leukotriens. Recent studies have shown that sPLA2 is synthesized and released by different cells, including liver and endothelial cells, and macrophages, when stimulated by TNF, IL-1, and IL-6. Redi et al. showed a reduction of sPLA2 with anti-TNF antibodies in a bacteremic baboon model, indicating that TNF also is able to induce in vivo the release of PLA2. Our findings suggest that IL-1 may not be an important cytokine in inducing sPLA2 release in lethal hypotensive shock. Alternatively, considering that a significant release of sPLA2 after IL-1ra administration was not observed until after 8 hours, we believe we may have missed an effect of IL-1 receptor blockade on the release of sPLA2 in the septic baboons because such an effect would not be expected to occur before 10 hours after the E coli challenge, ie, 8 hours after the appearance of IL-1β in the circulation. However, because of the lack of a sufficient number of blood samples in the control group after this time (most animals in the control group had died), we could not analyze a possible effect after 12 hours.

Although IL-1ra infused with a lethal dose of E coli protected all six animals thus treated (whereas in the control group, three of the five animals died within 24 hours), human considerations prevented observations with respect to survival beyond 24 hours. It can only be speculated that, considering that IL-1ra improves long-term survival after lethal endotoxemia in rabbits and mice, the treated baboons would have been long-term survivors. This limits the conclusions that can be drawn regarding the longer-term benefits of attenuation of the hemostatic and inflammatory parameters reported here. However, the data do allow the conclusion that the development of lethal complications was at least delayed in the treatment group, which may have been caused by the mitigating effects of IL-1ra on these parameters.

The model of sepsis used in this study reflects events after a single lethal injection of live E coli, whereas in patients, sepsis usually develops over a period of hours or even days, possibly because of a sustained release of bacteria and/or endotoxin into the circulation. Also, by the time sepsis is diagnosed in patients, the major catalyzing effects of IL-1 may already have taken place. Furthermore, in patients with sepsis, endogenously produced IL-1ra may contribute to control circulating or local IL-1 activity. Blockade of the effects of IL-1 by exogenous IL-1ra would then prove to be beneficial only in subpopulations of severely ill septic patients, especially those exhibiting a sustained release of IL-1. In a recent phase III clinical trial evaluating the effects of IL-1ra administration in patients with sepsis syndrome, predominantly patients with a high predicted risk of mortality tended to benefit from this treatment. Moreover, we recently performed a study in a subgroup of the phase III trial and observed that IL-1ra dose-dependently decreased activation of the coagulation and fibrinolytic systems and reduced the release of elastase and sPLA2 in agreement with the results reported here. These combined results indicate that in human sepsis, similar to the baboon model, IL-1 contributes to activation of various mediators. Presumably, the relative ineffectiveness of IL-1ra in human sepsis is related to the duration of the therapy because we found that levels of inflammatory parameters were similar to those of the placebo group after withdrawal of IL-1ra, suggesting that this drug was given too briefly in most patients. However, it should be noted that considering the difficulty in characterizing patient populations and the limitations of animal models, the ultimate significance of attenuation of these parameters is uncertain and warrants further investigations.
We conclude that exogenous administration of IL-1α to baboons resulted in an inflammatory response that consisted of the release of other cytokines,11 activation of coagulation and fibrinolysis, and the release of sPLA2. Furthermore, in a lethal primate model of sepsis, IL-1 receptor blockade reduced activation of coagulation and fibrinolysis, degranulation of neutrophils, and, possibly, the release of sPLA2. These findings indicate an important role of IL-1 in activating various other inflammatory mediators in lethal sepsis.

REFERENCES
21. Figari IS, Mori NA, Palladino MA: Regulation of neutrophil...
migration and superoxide production by recombinant tumor necrosis factors-alpha and beta: Comparison to recombinant interferon gamma and interleukin-1 alpha. Blood 70:979, 1987

31. Kharazmi A, Nielsen H, Bendtzen K: Recombinant interleukin-1α and β prime human monocyte superoxide production but have no effect on chemotaxis and oxidative burst response of neutrophils. Immunobiology 177:32, 1988


36. Dennis EA: Regulation of eicosanoid production: Role of phospholipase and inhibitors. Biotechnology 5:1294, 1987


Contribution of interleukin-1 to activation of coagulation and fibrinolysis, neutrophil degranulation, and the release of secretory-type phospholipase A2 in sepsis: studies in nonhuman primates after interleukin-1 alpha administration and during lethal bacteremia

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