Angiotensin II Increases Host Resistance to Peritonitis

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Studies by other laboratories have shown that angiotensin II (AII) can affect the function of cells which comprise the immune system. In the present study, the effect of AII on the function of peritoneal macrophages and peripheral blood monocytes was assessed. In vitro exposure (4 h prior to assay) of peritoneal macrophages from mice and rats to AII increased the percentage of cells that phagocytosed opsonized yeast and the number of yeast per macrophage. Furthermore, AII increased the respiratory burst capacity of peritoneal macrophages from mice and rats and peripheral blood mononuclear cells from humans. Because of these observations, the effect of AII on host resistance to bacterial infection was assessed. Intraperitoneal administration of AII was shown to increase host resistance (reduced abscess formation) in an animal model of bacterial peritonitis. Studies were then conducted to assess whether parenteral administration of AII, a clinically relevant route, could affect peritoneal host resistance in a manner similar to that observed after peritoneal administration. These studies showed that subcutaneous administration of AII throughout the postinfection interval increased the level of host resistance to bacterial peritonitis. Furthermore, in a study which compared AII and Neupogen, an agent approved for use for the reduction of febrile neutropenia after myeloablative therapy, daily subcutaneous administration of AII reduced abscess size and incidence, whereas Neupogen did not have any therapeutic benefit in this model. These data suggest that AII may be of therapeutic benefit as an immunomodulatory agent.

Angiotensin II (AII) is a product of the renin-angiotensin system which plays an important role in the regulation of blood pressure and fluid and electrolyte balance (49). However, this eight-amino-acid peptide does not exclusively control blood pressure; it has also been shown to modulate wound repair in several animal models. Rodgers et al. (35) found that administration of AII accelerated the repair of full-thickness excisional wounds in healthy and impaired rats, as well as diabetic mice. Furthermore, it has been shown that administration of AII accelerated the healing of partial-thickness burns (36). More recently, AII has been shown to act as a hematopoietic factor in the acceleration of the recovery of white blood cells and survival after myeloablative therapy (K. E. Rodgers et al., unpublished data). It is conceivable that the survival benefit was due to increased leukocyte function and subsequent host resistance to infection. The studies described here were conducted to test this hypothesis.

Prabha et al. (32) first observed that AII, when tested at physiological concentrations, can increase free-radical generation by polymorphonuclear neutrophils (PMNs). This observation was confirmed by Kumar and Das (22). Hydrogen peroxide is an important component in the respiratory burst system that can be used to measure increased activation of neutrophils and macrophages. Based on these studies and studies conducted in this laboratory, AII not only may lead to a decrease in the half-life of prostacyclin and endothelium-derived vascular relaxing factor but also may contribute to the wound repair, infection prevention, and immunoregulation. AII has been shown to modulate murine macrophage Fc receptor activity (6) and phagocytosis (13) and has been shown to inhibit macrophage migration (50). AII has also been shown to play a role in human granulomatous inflammation (44). For example, AII was shown to be chemotactic for murine splenocytes and mononuclear phagocytes derived from mice infected with chromosomiosis (51, 52) and to augment gamma interferon production from human blood mononuclear cells (10). As AII has been shown to stimulate leukocyte function and may modulate functions involved in host resistance to infection, the effect of this peptide on leukocyte function in multiple species and on host resistance to bacterial peritonitis was evaluated.

MATERIALS AND METHODS

Materials. AII was purchased from Bachem (Torrance, Calif.) and was manufactured under Good Manufacturing Procedures. Neupogen was purchased as a pharmaceutical preparation (Amgen, Thousand Oaks, Calif.). All chemicals were of reagent or tissue culture grade and were purchased from Sigma Chemical Co. (St. Louis, Mo.).

Assessment of phagocytic capability. Resident peritoneal macrophages were harvested from C57BL/6 mice or Sprague-Dawley rats and were resuspended at a concentration of 106 cells/ml in phosphate-buffered saline (PBS). An aliquot (0.5 ml) of cells was placed on a glass coverslip in a 35-mm petri dish (38, 40). Prior to incubation in an incubator, 0.5 ml of PBS or various concentrations of AII (final concentration, 1 to 1,000 μg/ml) was added to the individual coverslips. The dishes containing the coverslips were then placed in the incubator at 37°C for 4 h. At the end of this time, the coverslips were then washed three to six times with PBS, and opsonized yeast particles (yeast opsonized with adult serum from the same species as that under study) were added to the coverslips. This incubation was allowed to proceed for 2 h. At the end of this incubation, the coverslip was again washed with PBS and was inverted onto a glass slide. The number of macrophages that ingested yeast and the number of yeast ingested per macrophage were then determined microscopically. At least 100 macrophages per coverslip were counted.

Assessment of respiratory burst activity. The murine or rat peritoneal cells were harvested by lavage with 5 to 15 ml of cold PBS with 0.5% bovine serum albumin. The human peripheral blood mononuclear cells were harvested by venipuncture from healthy human volunteers and were isolated from peripheral blood by Ficoll-Hypaque density centrifugation. After isolation, the cells were resuspended at 105 cells/ml and were placed at 100 μl per well into 96-well plates (37, 38). The cells were incubated with various concentrations of AII for 4 h at 37°C. The viability of the cells was assessed by trypan blue exclusion. The cells were then preloaded with the fluorescent probe for hydrogen peroxide, 2,7 dichlorofluorescein acetate (nonfluorescent in the absence of hydrogen peroxide). Fifteen minutes later, 10 μg/ml of phenol myristate acetate (PMA) or PBS (without PMA) was added to stimulate the production of hydrogen peroxide. In the absence of PMA or peptide, no hydrogen peroxide production is observed.
One hour after stimulation, the level of fluorescence produced was measured on a Cytofluor 2350 multwell fluorometer.

**Study of host resistance to bacterial peritonitis.** (i) Animals. Female Sprague-Dawley rats (Weight, 175 to 225 g) were used for this study (89). The rats were acclimatized for at least 2 days prior to surgery. The rats were housed in the University of Southern California Vivarium (an American Association for Laboratory Animal Certification-certified and -accredited facility) on a 12-h light and 12-hour dark cycle. Food and water were available ad libitum except in the immediate postoperative interval. In the initial study, AII was administered via an Alzet pump placed subcutaneously with a tube leading to the peritoneal cavity. In a subsequent study, AII was administered daily by subcutaneous or intraperitoneal injection with and without pretreatment by subcutaneous injection. In the final study, the animals were pretreated for 3 days prior to implantation for infection and every day after injection with either AII (1 to 100 μg/kg of body weight/day) or Neupogen (0.1 to 10 μg/kg/day) by subcutaneous injection once daily.

(ii) Preparation of gelatin capsules. Theecal contents and feces from rats fed hamburgher for 2 weeks were collected and mixed 1:1 with sterile peptone yeast glucose broth containing no preservatives (Scott Laboratories) and 10% barium sulfate (31). The amount of this fecal preparation that caused mortality in 0 to 20% of the rats (75 μl) was determined and was aseptically added to a gelatin capsule (Number 1; Eli Lilly & Company). This capsule was then placed in a second larger capsule (Number 00; Eli Lilly & Company). This was referred to as a double-walled gelatin capsule. The capsules were prepared 1 week prior to implantation and were stored under frozen conditions under quarantine until the day of surgery.

(iii) Implantation of gelatin capsule. The rats underwent a standardized procedure for laparotomy (intramuscular anesthesia with ketamine-xylazine [Rompun], shaving with animal clippers, betadine scrub, alcohol scrub). A 2-cm incision was then made in the midline. A double-walled gelatin capsule was placed through the incision on the right side of the abdomen. The abdominal wall and skin were then sutured closed by using two layers of 4-0 Ethilon suture. Following surgery, the rats received analgesic for 3 days and were observed twice daily for signs of morbidity or mortality (36; K. E. Rodgers et al., in press).

(iv) Treatment with AII and Neupogen. The animals were treated with AII via several routes. In an initial study, AII was administered via an Alzet minimicrosyringe pump (0.5 μg/h; the pump can administer drug for 14 days) via a polyethylene tube that was placed in the abdominal cavity and that allowed continuous administration until necropsy. In subsequent studies, the effects of AII administered by intraperitoneal or subcutaneous injection was assessed. In the final study, the effects of AII and Neupogen administered subcutaneously were assessed.

(v) Necropsy. The rats that died during the 11-day postoperative observation period were necropsied to confirm the presence of an acute bacterial infection (36). The rats that survived the initial acute infection were killed on day 11 after surgery. Each rat was examined for the following: the ability of an investigator to palpate any abdominal abscesses through the skin, odor upon opening, and splenomegaly. In addition, four areas of the peritoneum were examined for abscess formation. These areas included the liver, abdominal wall, bowel, and omentum. The percentage of abscess-free sites was calculated as [number of sites evaluated without abscess (number of animals × 4 sites)] / 100. The abscesses were scored at each site as follows: 0, no abscess present at the site; 0.5, one very small abscess present at the site; 1, several small abscesses present at the site; 2, medium abscess present at the site; 3, large or several medium abscesses present at the site; 4, one very large or several large abscesses present at the site. The scoring was conducted in a blinded fashion by two separate observers, and the scores were recorded.

**Statistics.** The effect of AII on the function of leukocytes was evaluated by Student’s t test and Duncan’s multiple range test. The incidence of abscess formation was analyzed by the chi-square test. The data from the abscess evaluation were analyzed by rank order analysis followed by analysis of variance. Rank order analysis involved ranking of nonparametric data in ascending order, numbering of the scores in order, assignment of an equivalent rank to tied scores, and calculation of the mean and standard error of the rank.

**RESULTS**

**Effect of AII on phagocytic capability.** Resident peritoneal macrophages have very little phagocytic activity. Exposure of macrophages to inflammatory or activating agents will increase this macrophage function. The first study was conducted with the peritoneal cells of mice (Fig. 1). The cells were preincubated with AII during the adherence phase prior to addition of opsonized yeast. Exposure to 10 μg or more of AII per ml increased the phagocytic capability of peritoneal macrophages. Less than 1% of the cells in the resident population were phagocytic (0.01 yeast per cell observed). After exposure to AII this increased to over 25% phagocytic cells at the highest concentration, with, on average, one yeast observed per macrophage (25-fold increase in the number of macrophages able to phagocytose and a 100-fold increase in the number of particles phagocytized). A similar study was conducted with rat peritoneal leukocytes. In the second study, the effects of AII (100 to 1,000 μg/ml) on the phagocytic capability of rat macrophages were assessed. In Fig. 2, both concentrations of the peptide tested increased the phagocytic capability of rat macrophages. This suggests that AII will stimulate macrophage differentiation. Furthermore, phagocytosis is a function of macrophages that leads to the ingestion and clearance of bacteria and cellular debris.

**Effect of AII on respiratory burst activity.** The respiratory burst of leukocytes (macrophages and polymorphonuclear neutrophils) is one component of the mediator system used to kill bacteria. As with phagocytosis, the level of this functional activity in resident macrophages is low. With differentiation either to an elicited (inflammatory) or to an activated state, this functional activity is significantly elevated. Studies were conducted to assess the effect of in vitro exposure of murine or rat peritoneal macrophages and human peripheral blood mononuclear cells to various concentrations of AII on the capacity to generate oxygen radicals via the respiratory burst.
In all studies and all species, AII increased the ability of leukocytes (peritoneal macrophages in mice [Fig. 3] and rats [Fig. 4] or peripheral blood mononuclear cells in humans [Fig. 5]) to generate hydrogen peroxide both alone and in response to stimulation with PMA.

Effect of AII on bacterial peritonitis. In an initial study, the effect of continuous intraperitoneal administration of AII via an Alzet miniosmotic pump was assessed. A significant dose-dependent decrease in the incidence (Fig. 6) and sizes of the abscesses formed. Furthermore, a reduction in these same parameters was observed after subcutaneous or intraperitoneal administration of AII by daily injection and was further enhanced by pretreatment with AII (Fig. 7; Table 1).

Finally, the effect of AII on the resolution of bacterial peritonitis was evaluated and was compared with that of Neupogen (Fig. 8). Pretreatment with AII for 3 days followed by daily administration until necropsy significantly reduced the sizes of the abscesses that formed and the incidence of abscess formation in a dose-related fashion. That is, administration of 1 μg of AII per kg per day had reduced efficacy compared with administration of 10 and 100 μg/kg/day. On the other hand, Neupogen had no effect on the incidence or sizes of the abscesses that formed.

DISCUSSION

Previous studies have shown that angiotensin II can modulate leukocyte function. Numerous studies have shown that leukocytes bind to, in a nonsaturable manner, or interact with angiotensin II, suggesting a direct effect of this agent on the leukocyte (26). Many of the functions evaluated both in the literature and this report are involved in host resistance to bacterial infection. Therefore, the potential for a therapeutic benefit as a result of alterations in leukocyte function was evaluated in a model of bacterial peritonitis. This model has been used extensively in the development of broad-spectrum antimicrobials and reflects numerous clinical situations, including trauma to the gastrointestinal tract (ruptured appendix, appendectomy, bowel resection, gunshot or knife wound, trauma due to intraperitoneal catheterization, etc.). Evaluating...
tion of the effect of AII on abscess formation shows that the in vitro observation could be translated into a therapeutic benefit in this model. As AII acted on the host as an immunomodu- 
lar rather than on the bacteria, resistance to the effects on this molecule may not occur. This would be an advantage over antimicrobials, which allow the development of resistant strains. This observation should benefit not only individuals with normally functioning immune systems (as described here) but those with impaired immune systems as well, including patients undergoing immunosuppressive therapy (e.g., chemother- 
apy [antirejection drugs after transplantation]) or patients with human immunodeficiency virus infection. The fact that the responses observed very rapidly after in vitro exposure suggests a direct effect that does not require T-lym- 
phocyte involvement for the initial response.

The effect of AII on host resistance in this model was com- 
pared with that of Neupogen, a colony-stimulating factor (CSF) that has been approved for use for the control of febrile neutropenic episodes and that has been shown in numerous studies to modify neutrophil activity (45). CSFs are naturally occurring glycoproteins that increase the rates of production and matu- 
ration of hematopoietic precursors. Granulocyte CSF (G-CSF) or Neupogen is a recombinant cytokine currently used in clin- 
cal practice to replete neutrophils in neutropenic patients (2, 5, 7, 27, 30, 46). In clinical trials G-CSF has been shown to decrease infectious morbidity in compromised oncology and transplantation patients (14, 17, 43).

As G-CSF has been shown to (i) reduce level of antibiotic use and the number of febrile neutropenic episodes and (ii) stimulate the number, differentiation, and function of neutro- 
phils, which are the first leukocytes to appear at the site of infection and which play a role in the initial clearance of a bacterial infection, the effect of this cytokine on host resistance has been assessed in numerous animal models. In general, G-CSF was administered as a pretreatment and was shown to protect against mortality resultant from the infection when the treatment increased the neutrophil number and to have no effect on the course of the disease in situations in which the PMN number was not changed (1, 3, 8, 9, 12, 15, 16, 18, 21, 23, 24, 25, 47, 48). However, none of these studies addressed the effect of G-CSF on the resolution of bacterial peritonitis by survivors of the infection. In this study, daily administration of Neupogen did not affect abscess formation. In fact, after Neu- 
pogen administration the surviving animals displayed pro- 
longed signs of acute infection, such as ruffled fur and lethargy. In contrast, administration of AII significantly reduced the incidence and size of the abscesses found in the abdominal cavity, perhaps by increasing the leukocyte function. As AII does increase the neutrophil numbers in irradiated animals, the benefit of this peptide in compromised hosts may be even more profound than that in healthy animals (Rodgers et al., unpublished data).

Bacterial products and/or secondary inflammatory mediators induced by an infection are known to be potent stimuli for the production of G-CSF (28). Furthermore, inflammatory cytokines increase the levels of G-CSF mRNA and the levels of secretion of active G-CSF (11, 19, 20, 29, 33, 34, 42, 53, 54). However, the results of experiments that have investigated whether G-CSF enhances phagocytosis have been variable (4, 41). Phagocytic and bactericidal activities against Staphylococcus aureus were significantly enhanced after preincubation of neutrophils with G-CSF. The data reviewed imply that G-CSF could promote the recovery of the host from either local or systemic infections by enhancing the activity of preexisting leukocytes and/or by increasing the number of these cells.

In a previous study, AII was shown to be comparable to

### Table 1. Effect of administration of AII on the rank order analysis of abscess size

| Groupa | Rankb | Mean scorec |
|--------|--------|-------------|
| Control | 50.1 ± 1.25 | 9.0 ± 0.72 |
| Placebo | 51.8 ± 1.7 | 9.5 ± 0.65 |
| SQ/SQ | 25.0 ± 4.2 | 3.7 ± 0.62 |
| SQ Post | 30.9 ± 4.5 | 4.9 ± 0.72 |
| SQ/IP | 21.8 ± 4.8 | 3.3 ± 0.67 |
| IP Post | 26.3 ± 3.5 | 4.1 ± 0.42 |
| Pump | 11.8 ± 2.9 | 2 ± 2.42 |

a SQ/SQ, subcutaneous treatment pre- and postinfection; SQ Post, subcuta- 
eous treatment postinfection; SQ/IP, subcutaneous treatment preinfection and intraperitoneal treatment postinfection; IP Post, intraperitoneal treatment postinfection.
b Rank represents the mean and standard error of the rank of the scores.
c The mean score represents the arithmetic mean of the actual score given.
Neupogen in enhancing circulating white blood cell recovery at early time points, and the effect of ALL was more prolonged than that of Neupogen (Rodgers et al., submitted). This would indicate that in immunocompromised individuals, ALL may aid in infection control not only by restoration of the normal white blood cell concentration but also through modification of leukocyte function.

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