Effect of Central Administration of Interleukin-1 Receptor Antagonist on Protein Synthesis in Skeletal Muscle, Kidney, and Liver During Sepsis

Carolyn E. Lloyd, Mary Palopoli, and Thomas C. Vary

Inflammatory cytokines may mediate the host response to infection via central nervous system (CNS), endocrine, and/or paracrine pathways. The purpose of the present study was to determine whether intracerebroventricular (ICV) infusion of interleukin-1 receptor antagonist (IL-1ra) influences the effects of sepsis on protein metabolism in peripheral organs (skeletal muscle, kidney, and liver). A constant ICV infusion of IL-1ra (100 μg/h) or saline was begun immediately before the induction of sepsis or sterile inflammation and continued for 5 days. ICV infusion of IL-1ra did not alter protein metabolism in animals with a sterile abscess. Sepsis reduced muscle weight, protein content, and rates of protein synthesis in gastrocnemius. ICV infusion of IL-1ra attenuated the sepsis-induced loss of muscle mass and protein and the inhibition of protein synthesis in gastrocnemius by augmenting the translational efficiency. Similar results were observed in kidney, with respect to kidney weight, total protein, rates of protein synthesis, and translational efficiency. However, central infusion of IL-1ra did result in a small (12%) increase in the renal RNA content in either sterile or septic abscess rats. In liver, ICV infusion of IL-1ra prevented the sepsis-induced inhibition of protein synthesis and reduction in translational efficiency. These results suggest that central administration IL-1ra can modulate protein metabolism in peripheral organs during sepsis by preventing the sepsis-induced defects in the translational efficiency.

SEPSIS REMAINS a common complication in the critically ill patient after surgery or trauma. Trauma and sepsis initiate a pattern of physiologic and metabolic alterations characterized by an increase in oxygen consumption and alterations in fat, carbohydrate, and protein metabolism (for review, see Siegel and Vary[1] and Cooney et al[2]). Whereas both trauma and sepsis cause profound alterations in protein metabolism in many organs of the body, the effects of sepsis on protein metabolism are more pronounced and persist despite adequate nutritional support (for review, see (Siegel and Vary,[1] Vary,[3] Cerra et al[4,5]). Indeed, one of the earliest recognizable metabolic disturbances in septic patients is the negative nitrogen balance as reflected by an excessive excretion of urea and the corresponding loss of lean body mass.[1,3-5] Urea is synthesized to remove nitrogenous waste in the metabolism of amino acids by the liver. Amino acids used for urea synthesis are derived from the breakdown of proteins. As skeletal muscle comprises as much as 45% of body weight, changes in protein turnover in this tissue would be expected to have profound effects on whole-body nitrogen balance. Abnormalities of both protein synthesis and degradation have been described in muscles during sepsis (for review, see Vary[3,6]).

The mediators responsible for the changes in protein synthesis during sepsis most likely involve the overproduction of proinflammatory cytokines, tumor necrosis factor (TNF), interleukin-1 (IL-1), and/or IL-6. In this regard, a diminution of protein synthesis in gastrocnemius is observed after acute or chronic infusion of IL-1,[7-10] suggesting that IL-1 plays a role in the sepsis-induced inhibition in protein synthesis in muscle. Furthermore, infusing a specific interleukin-1 receptor antagonist (IL-1ra) for 70 hours attenuated the hypoaminoacidemia and accelerated urea production observed in septic patients.[11] Collectively, these studies provide evidence that IL-1 is an important mediator of sepsis-induced alterations in protein metabolism.

Although these studies implicate peripheral effects of IL-1, there is growing evidence that cytokines in the brain may be important in mediating the peripheral effects of systemic bacterial infections. The potential participation of brain cytokines in the host's integrated responses to bacterial infection is suggested by detection of IL-1 in neurons and non-neuronal cells in rat brain and within the cerebrospinal fluid after a septic[12] or endotoxin challenge[13,14] or meningitis.[15] Furthermore, intracerebral administration of IL-1 produces a metabolic response similar to that observed during systemic infection[16] and mimics transiently the pyrexia and anorexia associated with infection.[17] Hill et al[18,19] have shown that chronic exposure of the central nervous system (CNS) to IL-1 can induce protein catabolism (as measured by weight loss and a negative nitrogen balance) in rats. Moreover, central administration of a specific IL-1ra attenuates some, but not all, of the metabolic responses secondary to systemic infection or endotoxin.[16,20-22] Hence, IL-1 in the brain may mediate some of the systemic responses resulting from a peripheral infusion of IL-1 or endogenous IL-1 production after infection.

However, there is little information regarding the effects of central administration of IL-1ra on protein synthesis in organs peripheral to the brain during sepsis. In the present set of experiments, a specific receptor antagonist for IL-1 (IL-1ra) was administered intracerebraventricularly at the time of induction of sepsis to ascertain the potential role of central IL-1 in mediating the effects of sepsis on protein synthesis in skeletal muscle, liver, and kidney.

MATERIALS AND METHODS

Experimental Protocols

Adult male Sprague-Dawley rats were maintained on a 12:12 hour light:dark cycle with water and standard rat chow provided ad libitum

From the Department of Cellular and Molecular Physiology, Pennsylvania State University College of Medicine, Hershey, PA.

Submitted January 25, 2003; accepted March 12, 2003.

Supported by National Institute of General Medical Sciences (NIGMS) Grant No. GM-39277 from the National Institutes of Health.

Address reprint requests to Thomas C. Vary, PhD, Department of Cellular and Molecular Physiology, Rm C4710, Penn State University College of Medicine, 500 University Dr, Hershey, PA 17033.

0026-0495/03/5209-0049$30.00/0

doi:10.1016/S0026-0495(03)00161-6

for at least 1 week before the experimental protocol. On the day of the experiment, rats were randomly divided into 4 groups: sterile (n = 8); sterile + IL1ra (n = 6); septic (n = 7); and septic + IL1ra (n = 10). Subsequently, stereotaxic surgery was performed on all animals to implant a cannula unilaterally into the lateral ventricle of the brain as described previously in our laboratory.[20,21] Briefly, rats weighing 200 to 300g were anesthetized with a combination of ketamine (110 mg/kg body weight) and acepromazine (1 mg/kg body weight). An intracerebral cannula connected to an Alzet minipump was placed stereotaxically into the ventricle for an intracerebroventricular (ICV) infusion of either IL-1ra (100 μg/h) or an equal volume of the vehicle.[20,21] The minipump was placed subcutaneously in the intrascapular space, and the wound was sutured. We have previously used this approach to examine the role of central IL-1 in mediating the endotoxin-induced changes in peripheral glucose metabolism[20] and insulin-like growth factor (IGF)-I system.[21]

With the animals anesthetized, sepsis was then induced by implanting a fecal-agar pellet inoculated with 10^5 colony-forming units (CFU) *Escherichia coli* (*E coli*) and 10^9 CFU *B fragilis* into the abdominal cavity.[23-26] Control animals (sterile) were implanted with a sterile fecal-agar pellet, generated by replacing the bacteria inoculum with sterile saline.[23-26] The intra-abdominal abscess was allowed to develop for 5 days. Both nonseptic inflammatory and septic rats develop an abdominal abscess and show leukocytosis; however, the magnitude of the leukocytosis is 2-fold greater in the septic animals.[27] Bacteremia is not observed in rats with a sterile abscess.[28] Introduction of the infected fecal-agar pellet results in a hyperdynamic, hypermetabolic septic condition, which is not observed in rats with the sterile abscess.[29] Furthermore, animals with a sterile abscess exhibit growth curves similar to those observed in nonoperated, pair-fed control animals, and rates of protein synthesis in gastrconemius are indistinguishable from those observed in non-operated, pair-fed control animals.[25] However, rats with a sterile abscess exhibit a stimulation of hepatic protein synthesis, consistent with an acute-phase response compared with non-operated, pair-fed control animals.[38,39]

We have previously established that rats with either sterile abscess or septic abscess have reduced food intake in the first 2 days postsurgery compared with rats fed ad libitum.[30,31] Thereafter, rats with a sterile or septic abscess consume the same amount of food on a daily basis as rats fed ad libitum. There were no significant differences in food intake between the sterile abscess and septic abscess rats over the course of abscess formation.

Protein Synthesis

The rate of protein synthesis in vivo was measured by the incorporation of radioactive phenylalanine into protein using the modified flooding-dose technique as previously described.[8,32-34] Five days after implanting the fecal agar pellet, animals from all 4 groups were anesthetized as described above, and a polyethylene catheter (PE 50 tubing) was surgically inserted into the carotid artery. A bolus infusion of [^{3}H]-L-phenylalanine (Phe) (150 mmol/L, 30 μCi/mL; 1 mL/100 g body weight) was given via the jugular vein. At 2, 6, and 10 minutes after injection of the radioisotope, blood samples (1 mL) were withdrawn, centrifuged, and the plasma retained for measurement of phenylalanine concentrations and radioactivity.[8,32-34] Immediately after the removal of the 10-minute blood sample, the gastrocnemius, kidney, and liver were sequentially excised, weighed, and frozen between aluminum blocks precooled to the temperature of liquid nitrogen. All tissues were stored at −85°C until analysis.

The frozen tissue samples were powdered under liquid nitrogen with a mortar and pestle and a portion was used to estimate the amount of [^{3}H]phenylalanine incorporated into total mixed protein as previously described.[8,32-34] The specific radioactivity of phenylalanine in the plasma was measured by high-performance liquid chromatography

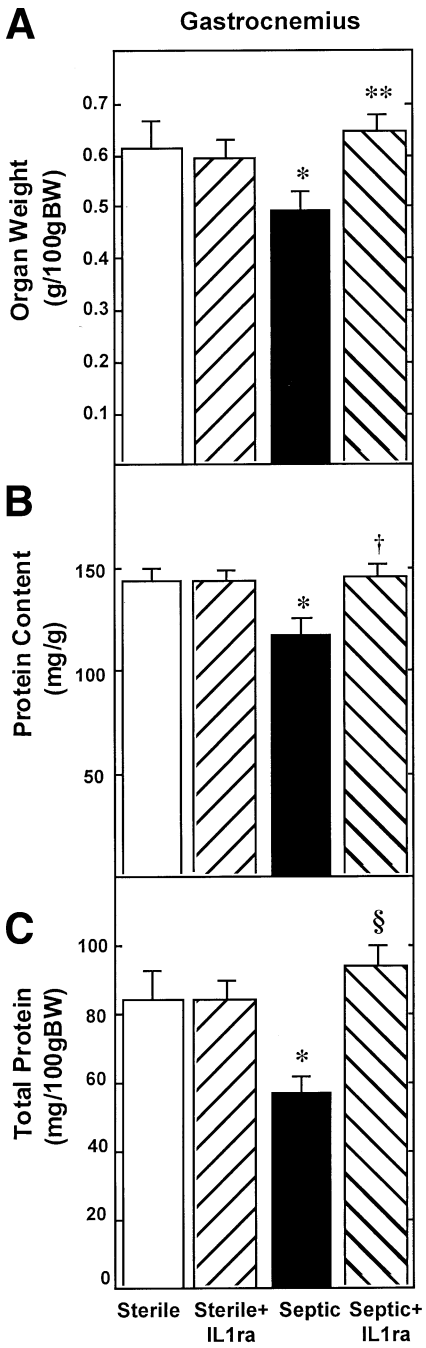

Fig 1. Effect of central administration of IL-1ra on (A) gastrocnemius weight, (B) protein content, and (C) total protein/muscle. The gastrocnemius was excised, frozen, and weighed from animals 5 days after the intraperitoneal introduction of the fecal-agar pellet containing either saline or *E coli* + *B fragilis* in rats receiving an intracerebral infusion of saline or IL-1ra as described in Materials and Methods. To measure the protein content, a portion of the frozen muscle was homogenized and the protein concentration in the homogenate measured by Biuret method. Total protein per gastrocnemius was calculated by multiplying the protein content by the weight of the gastrocnemius. Values shown are means ± SE for 6 to 10 animals in each group. *$P < .05$ *v* sterile, **$P < .05$ *v* septic, †$P < .01$ *v* septic, §$P < .05$ *v* septic (gastrocnemius weight ANOVA $F = 3.12$, $P < .05$; protein content ANOVA $F = 4.98$, $P < .01$; total protein\ANOVA $F = 7.02$, $P < .005$).

analysis of supernatants from trichloroacetic acid (TCA) extracts of the plasma.[35] The specific radioactivity from the 3 time points was averaged. Rates of protein synthesis were calculated by dividing the amount of [^{3}H]phenylalanine incorporated in protein per hour by the mean specific radioactivity of the plasma phenylalanine as the precursor pool. The protein content in tissue homogenates was measured using the Biuret method with crystalline bovine serum albumin used as a standard.

RNA

Total RNA was measured from homogenates of muscle samples. Briefly, 0.3 g of frozen, powdered tissue was homogenized in 5 vol of ice cold 10% TCA. The homogenate was centrifuged at 10,000 × *g* for 11 minutes at 4°C. The supernatant was discarded and the remaining pellet mixed in 2.5 mL of 6% (wt/vol) perchloric acid (PCA). The sample was centrifuged at 10,000 × *g* for 6 minutes at 4°C, the supernatant discarded, and the procedure repeated. Then, 1.5 mL of 0.3 N potassium hydroxide (KOH) was added to the pellet, and the samples were placed in a 50°C water bath for 1 hour. Samples were then mixed with 5 mL of 4 N PCA and centrifuged at 10,000 × *g* for 11 minutes. The concentration of RNA was determined by absorbance at 260 nm corrected by the absorbance at 232 nm as previously described.[25,26,36-38] Total RNA is expressed as milligram RNA/g tissue.

Statistical Analysis

Values shown are means ± SEM. Statistical evaluation of the data was performed using analysis of variance (ANOVA) to test for overall differences among groups, followed by the Student-Newman-Keuls test for multiple comparisons to determine significance between means only when ANOVA indicated a significant difference among the group means. Differences among the means were considered significant when *P* was less than .05.

RESULTS

Gastrocnemius Protein Synthesis

Infusion of IL-1ra into the brains of animals with a sterile abscess did not significantly reduce the weight, protein content, or total protein of the gastrocnemius (Fig 1A). Sepsis diminished the weight, protein content, and total protein of the gastrocnemius by 20%, 19%, and 33%, respectively. Infusion of IL-1ra into the brains of animals with a septic abscess prevented the sepsis-induced decrease in the weight, protein content, and total protein of the gastrocnemius. There were no significant differences between rats with a sterile abscess and septic abscess treated with IL-1ra in any of the weights or protein content.

Rates of protein synthesis in gastrocnemius were not significantly altered in animals with a sterile abscess infused ICV with IL-1ra compared with animals infused with saline (Fig 2A). Sepsis resulted in a 65% decrease in the rate of protein synthesis compared with rats with a sterile abscess infused with saline, which was prevented by the intracerebral infusion of IL-1ra. There were no significant differences in the rate of protein synthesis between sterile abscess and septic abscess rats treated with IL-1ra.

Total muscle RNA content and translational efficiency in gastrocnemius of animals with a sterile abscess and septic abscess both with and without intracerebral IL-1ra infusion were measured to examine potential mechanisms for alterations in rates of protein synthesis. The total RNA content in gastroc-

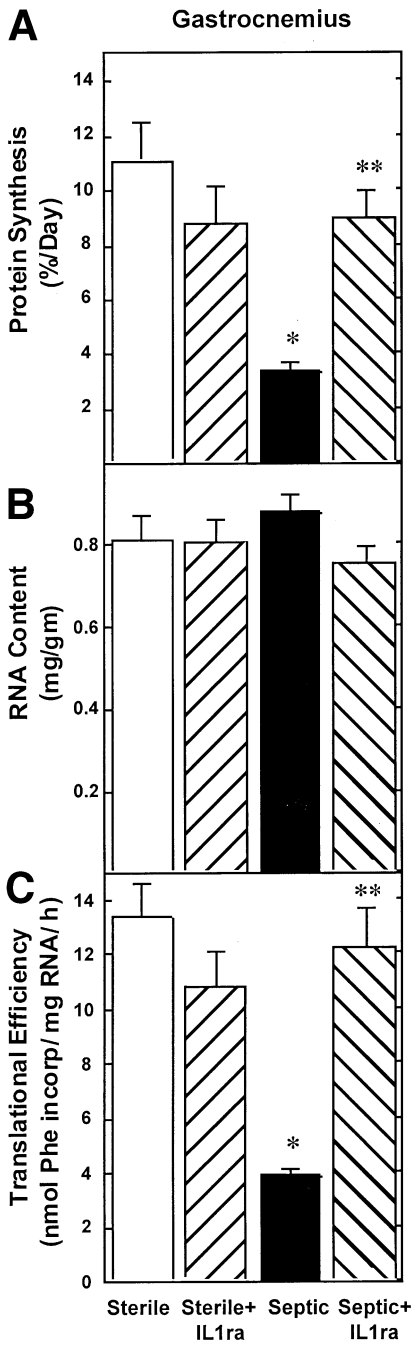

Fig 2. Effect of central administration of IL-1ra on (A) protein synthesis, (B) RNA content, and (C) translational efficiency in gastrocnemius. Rates of protein synthesis in gastrocnemius from animals described in Fig 1 were measured in vivo after intravenous injection with saline containing [^{3}H]phenylalanine (150 μmol/100 g body weight; 1 mL/100 g body weight). Measurement of [^{3}H]phenylalanine incorporation into muscle protein and calculation of rates of protein synthesis were performed as described in Materials and Methods.RNA was measured in muscle homogenates from the gastrocnemius as described in Materials and Methods. The translational efficiency was estimated by the rate of protein synthesis expressed relative to the muscle RNA.Values shown are means ± SE for 6 to 10 animals in each group. *$P < .001$ *v* sterile; **$P < .01$ *v* septic (protein synthesis ANOVA $F = 8.81$, $P < .0005$; translational efficiency ANOVA $F = 11.21$, $P < .0001$).

nemius from saline or IL-1ra infused rats is shown in Fig 2B. There were no significant differences in the total RNA content in gastrocnemius under any of the conditions examined. The translational efficiency is calculated by dividing the rate of protein synthesis by the muscle RNA content. Infusion of IL-1ra in rats with a sterile abscess did not alter the translational efficiency (Fig 2C). The translational efficiency was significantly decreased (~70%) in the gastrocnemius of septic rats infused with saline compared with rats with a sterile abscess. ICV infusion of IL-1ra into septic rats significantly enhanced the translation efficiency in gastrocnemius (~2.5-fold) compared with saline-infused rats.

Renal Protein Synthesis

The kidney organ weight was not significantly altered by central infusion of IL-1ra in rats with a sterile abscess, but was reduced in saline-infused septic rats (Fig 3A). ICV infusion of IL-1ra into animals with a septic abscess prevented the sepsis-induced decrease in kidney weight. There were no significant differences in kidney weight between animals with a sterile abscess and septic abscess treated with IL-1ra. The protein content of the kidney was not significantly different in any of the conditions examined (Fig 3B). However, the decrease in the kidney weight during sepsis caused an overall reduction in the amount of kidney protein (Fig 3C) that was prevented by ICV infusion of IL-1ra in animals with a septic abscess. There were no significant differences in total protein per kidney between sterile abscess and septic abscess rats treated with IL-1ra.

Rates of protein synthesis in the kidney were not significantly altered in animals with a sterile abscess infused with IL-1ra ICV compared with animals infused with saline (Fig 4A). Sepsis resulted in a 50% reduction in the rate of renal protein synthesis. However, ICV infusion of IL-1ra prevented the decline in renal protein synthesis observed in septic animals infused with saline. No significant differences in the rate of renal protein synthesis between nonseptic and septic abscess rats treated with IL-1ra were observed.

There were no significant differences in the total RNA content in kidneys from sterile abscess and septic abscess rats infused with saline (Fig 4B). Infusion of IL-1ra into the brain resulted in a small increase the renal RNA content in both sterile abscess (+12%) and septic abscess (+12%) rats compared with animals infused with saline. The translational efficiency in kidneys from nonseptic and septic rats infused with and without IL-1ra is shown in Fig 4C. Infusion of IL-1ra in rats with a sterile abscess did not affect the translational efficiency. However, the efficiency of translation was significantly decreased (~45%) in the kidneys of septic rats infused with saline compared with rats with a sterile abscess. ICV infusion of IL-1ra into septic rats significantly enhanced the translation efficiency in kidney (~2-fold) compared with saline-infused rats.

Hepatic Protein Synthesis

We have previously shown that weight of the liver is not significantly different in septic rats compared with sterile abscess controls.[38,39] Therefore, we did not measure the total liver weight in these animals. The septic insult or infusion of IL-1ra

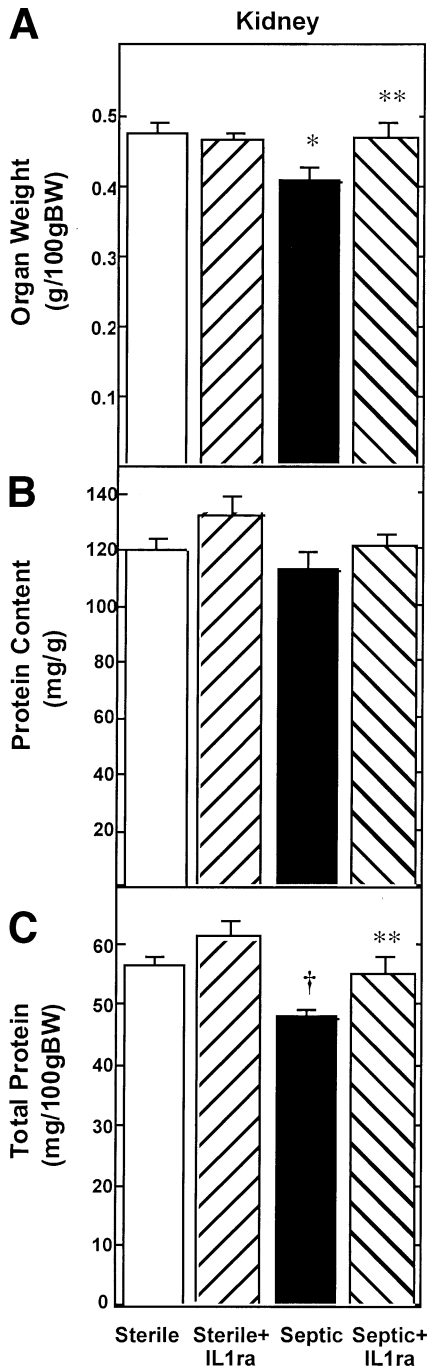

Fig 3. Effect of central administration of IL-1ra on (A) kidney weight, (B) protein content, and (C) total protein/kidney. The kidney was excised, frozen, and weighed from animals 5 days after the intraperitoneal introduction of the fecal-agar pellet containing either saline or *E coli* + *B fragilis* in rats receiving an intracerebral infusion of saline or IL-1ra as described in Materials and Methods. To measure the protein content, a portion of the frozen kidney was homogenized and the protein concentration in the homogenate measured by Biuret method. Total protein per kidney was calculated by multiplying the protein content by the weight of the kidney. Values shown are means ± SE for 6 to 10 animals in each group. *$P < .05$, †$P < .01$ *v* sterile; **$P < .05$ *v* septic (kidney weight ANOVA $F = 3.23$, $P < .05$; protein content ANOVA $F = 4.98$, $P < .01$; total protein ANOVA $F = 7.38$, $P < .001$).

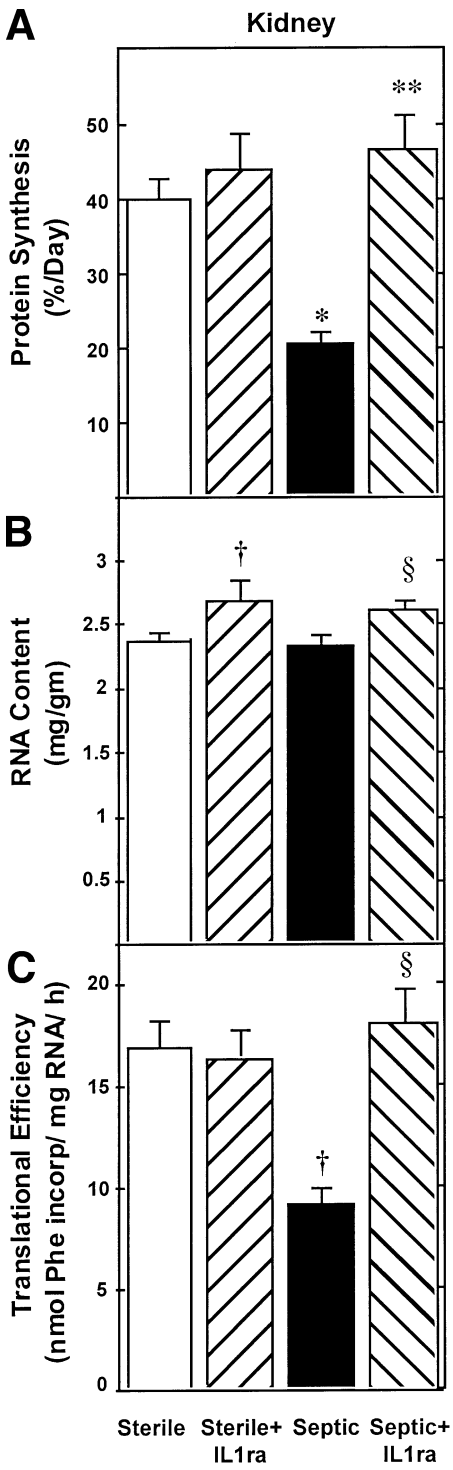

Fig 4. Effect of central administration of IL-1ra on (A) renal protein synthesis, (B) RNA content, and (C) translational efficiency. Rates of protein synthesis in kidneys from animals described in Fig 1 were measured as described in Fig 2. RNA was measured in kidney homogenates as described in Materials and Methods. The translational efficiency was estimated by the rate of protein synthesis expressed relative to the renal RNA content. Values shown are means ± SE for 6 to 10 animals in each group. *$P < .001$, †$P < .05$ *v* sterile; **$P < .001$, §$P < .05$ *v* septic (protein synthesis ANOVA $F = 8.81$, $P < .0005$; translational efficiency ANOVA $F = 11.21$, $P < .0001$).

did not significantly alter hepatic protein content (mg/g) compared with rats with a sterile abscess (sterile, 142 ± 12; sterile + IL1ra, 165 ± 9; septic, 137 ± 6; septic + IL1ra, 156 ± 6 mg/g wet wt).

Rates of hepatic protein synthesis were not significantly altered in rats with a sterile abscess infused ICV with IL-1ra compared with saline infused animals (Fig 5A). Sepsis caused a 32% decrease in the rate of hepatic protein synthesis compared with saline-infused sterile abscess rats. Intracerebral infusion of IL-1ra in rats with a septic abscess significantly increased the rate of hepatic protein synthesis 68% compared with untreated septic animals. There were no significant differences in the rate of hepatic protein synthesis between rats with a sterile abscess and septic abscess treated with IL-1ra.

There were no significant differences in the total hepatic RNA content in any of the conditions examined (Fig 5B). The translational efficiency in livers from sterile inflammatory and septic rats infused with and without IL-1ra is shown in Fig 5C. There were no significant differences in the rate of hepatic translational efficiency in sterile inflammatory rats treated with or without IL-1ra. The translational efficiency in untreated septic rats was reduced 45% compared with untreated rats with a sterile abscess, which was prevented by the intracerebral infusion of IL-1ra. There were no significant differences in the rate of hepatic protein synthesis between rats with a sterile abscess and septic abscess treated with IL-1ra.

DISCUSSION

IL-1 is an important mediator of many of the immunologic and metabolic responses to infection. Initially many investigations focused on the systemic administration of IL-1 because only activated cells of the monocyte-macrophage lineage were thought to produce this cytokine. However, IL-1 is present in the brain, as well.[12-16] Moreover, central administration of IL-1 is capable of modulating various aspects of peripheral metabolism, including glucose homeostasis,[20,40] endocrine alterations,[20,21] and nitrogen balance.[18,19] Hence, central IL-1 production may be an important mediator of the peripheral effects of bacterial infection.

The present study demonstrates that chronic infusion of IL-1ra into the brains of rats with an intra-abdominal bacterial abscess can modify the sepsis-induced derangements in protein synthesis in peripheral organs. In skeletal muscle, central administration of IL-1ra prevented the sepsis-induced loss of muscle mass and protein content. Part of the protein-sparing effect of central administration of IL-1ra during sepsis resulted from an attenuation of the inhibition of protein synthesis in this organ through prevention of the inhibition of translational efficiency.

Renal protein synthesis is unaffected by moderate stress, such as short-term fasting, laparotomy,[41]or aseptic inflammation.[39,42] Consistent with this observation, infusion of saline or IL-1ra into the brain of animals with a sterile abscess did not modify protein synthesis in kidney. However, there is virtually no information concerning the effects of sepsis on protein synthesis in kidney. Chronic sepsis caused the weight of the kidney to decrease over the course of the study period. The decreased kidney weight was accompanied by a diminished

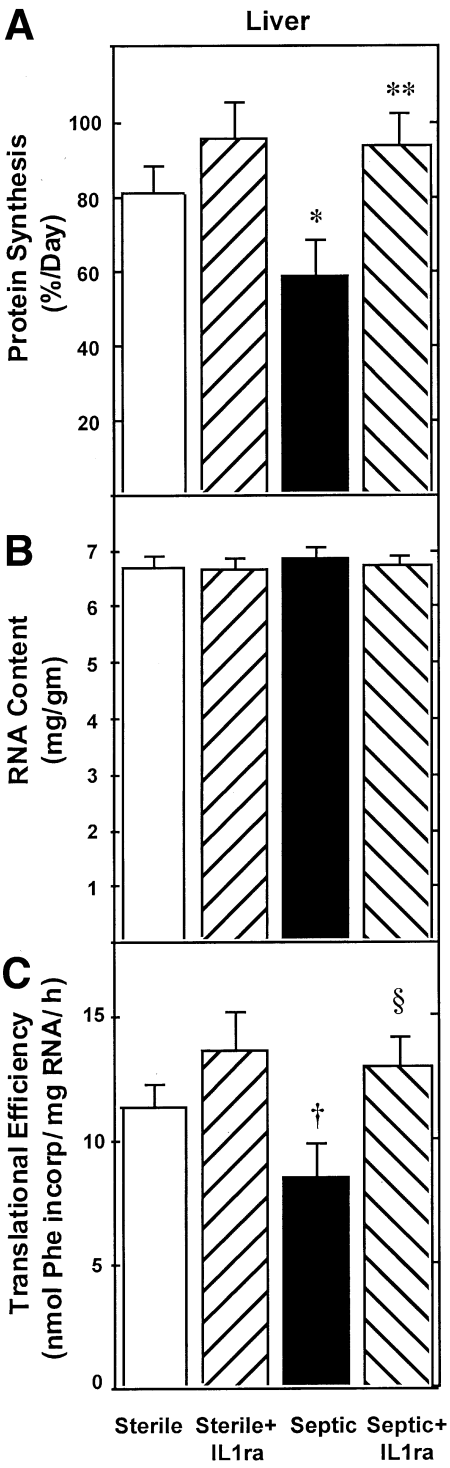

Fig 5. Effect of central administration of IL-1ra on (A) hepatic protein synthesis, (B) RNA content, and (C) translational efficiency. Rates of protein synthesis in livers from animals described in Fig 1 were measured as described in Fig 2. RNA was measured in liver homogenates as described in Materials and Methods. The translational efficiency was estimated by the rate of protein synthesis expressed relative to the hepatic RNA content. Values shown are means ± SE for 6 to 10 animals in each group. *$P < .05$, †$P < .01$ *v* sterile; **$P < .05$, §$P < .001$ *v* septic (protein synthesis ANOVA $F = 4.04$, $P < .05$; translational efficiency ANOVA $F = 7.78$, $P < .001$).

amount of protein per kidney. One potential explanation for this loss of kidney protein would be an inhibition of protein synthesis. Consistent with our previous reports,[39,42] renal rates of protein synthesis were significantly decreased by 50% in untreated septic rats. Infusion of IL-1ra intracerebraventricularly not only attenuated the decrease in kidney weight and protein content per kidney, but also prevented the inhibition of renal protein synthesis. ICV infusion of IL-1ra caused a small (12%) increase in the total RNA content in kidneys, a change not observed in skeletal muscle. The mechanism for this increase is not known. More importantly, IL-1ra prevented the decrease in renal protein synthesis by maintaining the translational efficiency in rats with a bacterial abscess. Indeed, the translational efficiency was increased over 2.5-fold in septic rats infused with IL-1ra compared with rats infused with saline.

Several cytokines including TNF, IL-1, and IL-6 have been implicated as modulators of hepatic protein synthesis during inflammation and sepsis.[7,34,43-45] Indeed, intravenous infusion of IL-1 for 5 days lowers rates of protein synthesis (Cooney and Vary, unpublished results). Rates of protein synthesis and the protein content are not significantly different in livers from rats with a sterile abscess and septic abscess, in accordance with our previous observations.[34,38,42,43] However, infusion of IL-1ra into the brain in septic rats resulted in a higher rate of hepatic protein synthesis compared with untreated septic animals. This result differs from what is observed after systemic infusion of IL-1ra into septic rats[6,43] or human volunteers,[46] in which intravenous infusion of IL-1ra in septic rats or endotoxin-treated humans did not significantly modulate the rate of hepatic protein synthesis or plasma content of acute phase proteins. The reason for the differential response in protein synthesis in central versus intravenous infusion of IL-1ra is not entirely obvious.

The mechanism by which central infusion of IL-1ra modulates protein metabolism is not completely understood. However, infusion of IL-1ra into the brain in septic rats or rats treated acutely with endotoxin does not modulate the septic-induced changes in plasma glucocorticoid concentrations.[20,21] Central administration of IL-1 may modulate the afferent and/or efferent vagus nerve signaling to target cells either by modulating the afferent signals to the hypothalamic-pituitary axis or efferent vagal output to cells and/or organs resulting in changes in lymphocyte response or cytokine production. Additional studies will be required to elucidate the precise role of central administration of IL-1ra on the peripheral response to sepsis.

The results of the present study extend previous studies examining the potential role of central IL-1 in mediating the effects of systemic bacterial infections. At equivalent doses, ICV infusion of IL-1, but not IL-6, caused negative nitrogen balance, weight loss, and anorexia.[18] The effects of ICV infusion of IL-1 were not solely mediated by glucocorticoids. Furthermore, the catabolic effects of IL-1 infused into the CNS cannot be accounted for totally by decreased food intake, indicating that IL-1 administration itself initiates a hypermetabolic state. We have previously shown that inhibition of protein synthesis in skeletal muscle contributes, in part, to the IL-1–induced derangements in protein metabolism.[8] In the present studies, the decreases in skeletal muscle and kidney weights

and protein content observed during sepsis were prevented by ICV infusion of IL-1ra. These alterations in tissue protein were caused, in part, by an inhibition in protein synthesis that was relieved by ICV infusion of IL-1ra. Furthermore, ICV infusion of IL-1ra prevented the sepsis-induced reductions in translational efficiency. Hence, correction of the inhibition of translational efficiency by ICV infusion of IL-1ra is sufficient to prevent the alterations in protein metabolism that develop during chronic sepsis.

ACKNOWLEDGMENT

The authors thank Gina Deiter for her expert technical assistance in performing these experiments.

REFERENCES

1. Siegel J, Vary T: Sepsis, abnormal metabolic control and multiple organ failure syndrome, in Siegel JH (ed): Trauma: Emergency Surgery and Critical Care. New York, NY, Churchill-Livingstone, 1987, pp 411-501

2. Cooney RN, Kimball SR, Vary TC: Regulation of skeletal muscle protein turnover during sepsis: Mechanisms and mediators. Shock 7:1-16, 1997

3. Vary TC: Regulation of skeletal muscle protein turnover during sepsis. Curr Opin Clin Nutr Metab Care 1:217-224, 1998

4. Cerra FB, Siegel JH, Coleman B, et al: Septic autocannibalism: A failure of exogenous nutritional support. Ann Surg 192:570-580, 1980

5. Cerra FB: Hypermetabolism-organ failure syndrome: A metabolic response to injury. Crit Care Clin 5:289-301, 1989

6. Vary TC: Interorgan protein and carbohydrate metabolic relationships during sepsis: Necessary evils or uncanny coincidences? Curr Opin Clin Nutr Metab Care 2:235-242, 1999

7. Balmer PE, McNurlan MA, Southorn BG, et al: Effects of human recombinant interleukin-1b on protein synthesis in rat tissues compared with classical acute-phase reaction induced by turpentine. Biochem J 279:683-688, 1991

8. Cooney RN, Maish III G, Gilpin T, et al: Mechanism of IL-1 induced inhibition of protein synthesis in skeletal muscle. Shock 11: 235-241, 1999

9. Fong Y, Moldawer LL, Marano M, et al: Cachectin/TNF or IL-1 alpha induce cachexia with redistribution of body proteins. Am J Physiol 256:R659-R665, 1989

10. Zamir O, Hasselgren P-O, Von Allmen D, et al: In vivo administration of IL-1ra induces muscle proteolysis in normal and adrenalectomized rats. Metabolism 42:204-208, 1993

11. Cooney R, Pantaloni A, Sarson Y, et al: A pilot study on the metabolic effects of IL-1ra in patients with severe sepsis, in Faist E. (ed): The 4th International Congress on the Immune Consequences of Trauma, Shock and Sepsis. Mechanisms and Therapeutic Approaches. Bologna, Italy, Mondozzi Editore, 1997, pp 909-912

12. Meyer TA, Wang JJ, Tiao GM, et al: Sepsis and endotoxin in mice stimulate the expression of interleukin-1 and interleukin-6 in the central nervous system. Clin Sci 92:S19-S25, 1997

13. Lieberman AP, Pitha PM, Shin HS, et al: Production of tumor necrosis factor and other cytokines by astrocytes stimulated with lipopolysaccharide or a neurotrophic virus. Proc Natl Acad Sci USA 86:6348-6352, 1989

14. Nakamori T, Morimoto A, Yamaguchi K, et al: Interleukin-Iβ production in rabbit brain during endotoxin-induced fever. J Physiol (Lond) 476:177-176, 1994

15. Mustafa MM, Lebel MM, Ramilo O, et al: Correlation of interelukin-1B and cachetin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. J Pediatr 115:208-211, 1989

16. Rothwell NJ, Luheshi G: Pharmacology of interleukin-1 actions in the brain. Adv Pharmacol 15:1-20, 1994

17. Plata-Salaman CR, French-Mullen JM: Intraventricular administration of s specific IL-1 receptor antagonist blocks food and water intake suppression induced by interleukin-1 beta. Physiol Behav 51: 1277-1279, 1992

18. Hill AG, Jacobson L, Gonzalez J, et al: Chronic central nervous system exposure to IL-1β causes catabolism in the rat. Am J Physiol 271:R1142-R1148, 1996

19. Hill AG, Siegel J, Rounds J, et al: Metabolic response to interleukin-1: Centrally and peripherally mediated. Ann Surg 225:246-251, 1997

20. Lang CH, Cooney RN, Vary TC: Central interleukin-1 partially mediates endotoxin-induced changes in glucose metabolism. Am J Physiol 271:E309-E316, 1996

21. Lang CH, Fan J, Wojnar MM, et al: Role of central IL-1 in regulating IGF-I during endotoxemia and sepsis. Am J Physiol 274: R956-R962, 1998

22. McHugh KJ, Collins SM, Weingarten HP: Central IL-1 receptors contribute to suppression of feeding after acute colitis in the rat. Am J Physiol 266:R1659-R1663, 1994

23. Vary TC, Kimball SR: Effect of sepsis on eIF4E availability in skeletal muscle. Am J Physiol 279:E1178-E1184, 2000

24. Vary TC, Jefferson LS, Kimball SR: Insulin fails to stimulate muscle protein synthesis in sepsis despite unimpaired signaling to 4E-BP1 and S6K1. Am J Physiol 281:E1045-E1053, 2001

25. Vary TC, Kimball SR: Sepsis-induced alterations in muscle protein synthesis: Differential effects on fast- and slow-twitch muscles. Am J Physiol 262:C1513-1519, 1992

26. Jurasinski CV, Kilpatrick L, Vary TC: Amrinone prevents muscle protein wasting during chronic sepsis. Am J Physiol 268:E491-E500, 1995

27. Vary TC, Murphy JM: Role of extra-splanchnic organs in the metabolic response to sepsis: Effect of insulin. Circ Shock 29:41-57, 1989

28. Vary TC, Siegel JH, Tall DH, et al: Role of anaerobic bacteria in intra-abdominal septic abscesses in mediating septic control of skeletal muscle glucose oxidation and lactic acidemia. J Trauma 29: 1003-1014, 1989

29. Nakatani T, Sato T, Marzella L, et al: Hepatic and systemic metabolic response to aerobic and anaerobic intra-abdominal abscesses in a highly reproducible chronic rat model. Circ Shock 13:271-294, 1984

30. Cooney R, Owens E, Jurasinski C, et al: Interleukin-1 receptor antagonist prevents sepsis-induced inhibition of protein synthesis. Am J Physiol 267:E636-E641, 1994

31. Vary TC, Siegel JH, Placko R, et al: Effect of dichloroacetate on plasma and hepatic amino acids in sterile inflammation and sepsis. Arch Surg 124:l07l-l077, 1989

32. Anthony JC, Gautsch T, Kimball SR, et al: Orally administered leucine stimulates protein synthesis in skeletal muscle of postabsorptive rats in association with increased eIF4F formation. J Nutr 130: 139-145, 2000

33. Cooney RN, Kimball SR, Eckman R, et al: TNF-binding protein ameliorates inhibition of skeletal muscle protein synthesis during sepsis. Am J Physiol 276:E611-E619, 1999

34. Cooney RN, Kimball SR, Maish G III, et al: Effects of TNF binding protein on hepatic protein synthesis during chronic sepsis. J Surg Res 93:257-264, 2000

35. Drenvich D, Vary TC: Analysis of physiologic amino acids using dabsyl derivatization and reverse-phase liquid chromatography. J Chromatogr 613:137-144, 1991

36. Jurasinski C, Vary T: Insulin-like growth factor-I accelerates protein synthesis during sepsis. Am J Physiol 269:E977-E981, 1995

37. Vary TC, Jurasinski CV, Karinch AM, et al: Regulation of eukaryotic initiation factor 2 expression during sepsis. Am J Physiol 266:E193-E201, 1994

38. Vary TC, Kimball SR: Regulation of hepatic protein synthesis in chronic inflammation and sepsis. Am J Physiol 262:C445-452, 1992

39. Vary TC, Owens E, Cooney RN: Prevention of skeletal muscle catabolism in sepsis does not affect visceral protein metabolism. Am J Physiol 270:E621-E626, 1996

40. Lang CH, Molina PE, Yousef KA, et al: Role of IL-1a in central nervous system immunomodulation of glucoregulation. Brain Res 624: 53-60, 1993

41. Preedy VR, Paska L, Sugden PH, et al: The effects of surgical stress and short-term fasting on protein synthesis in vivo in diverse tissues of the mature rat. Biochem J 250:179-188, 1988

42. Svanberg E, Frost RA, Lang CH, et al: Insulin-like growth factor-I (IGF-I)/IGF binding protein-3 complex attenuates sepsis-induced inhibition of protein synthesis in skeletal muscle of rats. Am J Physiol 279:E1145-E1158, 2000

43. Cooney RN, Owens E, Slaymaker D, et al: Prevention of skeletal muscle catabolism in sepsis does not impair visceral protein metabolism. Am J Physiol 270:E621-E626, 1996

44. Baumann H, Gauldie J: Regulation of hepatic acute phase plasma protein genes by hepatocyte stimulating factors and other mediators of inflammation. Mol Biol Med 7:147-159, 1990

45. Baumann H, Richards C, Gauldie J: Interaction among hepatocyte-stimulating factors, interleukin-1 and glucocorticoids for regulation of acute phase plasma proteins in human hepatoma (HepG2) cells. J Immunol 139:4122-4128, 1987

46. Van Zee KJ, Coyle SM, Calvano SE, et al: Influence of IL-1 receptor blockade on the human response to endotoxin. J Immunol 154:1499-1507, 1995