Metabolic Effects of Insulin and Insulin-Like Growth Factor-I in Endotoxemic Rats During Total Parenteral Nutrition Feeding

Pei Ra Ling, Erin Lydon, Zhensheng Qu, Robert C. Frederich, and Bruce R. Bistrian

The effects of insulin and insulin-like growth factor-I (IGF-I) on protein, energy, and glucose metabolism were examined in endotoxemic rats receiving total parenteral nutrition (TPN) for 3 days. The endotoxemic model was induced by constant infusion of lipopolysaccharide (1 mg/kg · d) for 3 days. The TPN regimen provided 200 kcal/kg · d and 1.5 g protein/kg · d. The dosage of insulin (5 mU/kg · h) and IGF-I (20 μg/kg · h), either alone or in combination, was chosen to maintain normal levels of leucine and glucose in plasma during feeding. One normal control and 4 endotoxemic groups with different treatments (saline, IGF-I, insulin, or IGF-I and insulin) were included. The effects of endotoxin were compared between the group receiving endotoxin alone and normal controls, and the effects of insulin and IGF-I were compared within the endotoxemic groups. The results show that endotoxin significantly increased the mortality and induced a hypermetabolic state, and nutrition alone could not overcome the catabolism induced by endotoxin. However, administration of insulin and IGF-I enhanced protein preservation in muscle tissue in endotoxemic rats during TPN. This effect was greater for insulin either alone or in combination with IGF-I. Insulin also significantly reduced the mortality. There were no additive effects of these two anabolic hormones on any measured parameter in these experimental conditions.

SEVERE INJURY, infection, and other critical illnesses are associated with excessive loss of body protein. A loss of greater than 10% of body protein contributes significantly to morbidity and debility.[1] Although intensive nutritional support using total parenteral nutrition (TPN) has provided beneficial effects in these patients, nutritional therapy alone cannot overcome the catabolic effects of severe illness.[2-4]

Resistance to the actions of anabolic hormones such as insulin, growth hormone, and insulin-like growth factor-I (IGF-I) appears to be a significant contributing factor in the catabolic response to severe illness. Therefore, the administration of anabolic hormones or growth factors has been considered a potential strategy to promote nitrogen accretion in patients who require TPN. Administration of insulin with TPN has routinely been used to maintain glucose homeostasis and enhance nutrient utilization in patients with diabetes or impaired glucose tolerance with hyperglycemia, especially with aggressive nutritional support in the setting of critical illness.[5]

Recent studies have shown that IGF-I attenuated dexamethasone-induced protein catabolism and increased insulin sensitivity in rats.[6] In addition, IGF-I is an effective anabolic agent in conditions of growth hormone resistance.[7,8] Human studies have also shown that combination treatment with IGF-I and growth hormone is more anabolic than treatment with either hormone alone,[9] suggesting both unique and complementary effects between IGF-I and growth hormone, because each uses a specific receptor. While IGF-I shares substantial structural and functional homology with insulin and exerts an anabolic function by binding to its own receptor, it is not clear whether the analogous rationale for administration of IGF-I and growth hormone together would also apply to IGF-I and insulin as related to the additive anabolic effects.

In this study, we compare the effects of insulin (5 mU/kg · h) and IGF-I (20 μg/kg · h), either alone or in combination, on protein, energy, and glucose metabolism and mortality in rats that received endotoxin infusion (1 mg/kg · d) and TPN (220 kcal/kg · d) for 3 days. The dosage of insulin and IGF-I was chosen to maintain normal plasma leucine and glucose levels during TPN, based on our pilot studies and a previous report[10] in normal rats. In addition, our previous studies demonstrated that nitrogen loss and the inflammatory response were persistent in this endotoxemic model even with nutritional support, mimicking the typical pattern of clinical infection. Although a longer period of infusion would be preferable, complications such as secondary infection often develop after 3 days of central venous feeding, which can complicate the interpretation of the results. Thus, the present study was limited to 3 days of anabolic hormone administration with TPN.

The results demonstrate that during TPN, each hormone and the combination significantly enhanced protein preservation in muscle tissue in endotoxemic rats. These effects were greater for insulin, either alone or in combination with IGF-I, compared with IGF-I alone. However, there were no additive effects of these two anabolic hormones on any measured parameter.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (weight, 250 to 280 g; Taconic Farms, Germantown, NY) were acclimated in individual cages in the animal facility of Beth Israel Deaconess Medical Center for 4 days prior to the experiments. During this period, animals were given free access to food and tap water.

On day 1 of the experiment, all animals underwent surgical placement of a jugular venous silastic catheter (0.025 in ID × 0.047 in OD) under ether anesthesia. The catheters were externalized in the midscapular region and attached to a flow-through swivel to permit free movement. After surgery, the animals were allowed to recover in individual cages for 24 hours, and saline solution was constantly infused (2 mL/h) through the catheter.

From the Laboratory of Nutrition/Infection, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

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Current address: R.C.F., Division of Endocrinology, Department of Medicine, University of Kentucky, Lexington, KY.

Address reprint requests to Bruce R. Bistrian, MD, PhD, Laboratory of Nutrition/Infection, Beth Israel Deaconess Medical Center, West Campus, One Deaconess Road, Boston, MA 02215.

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Experimental Design

On day 2 of the experiment, all animals were individually housed in metabolic cages and received TPN support for the next 3 days. During these 3 days of TPN feeding, rat chow was removed from the cages. The parenteral regimen supplied 220 kcal/kg · d, 1.5 g nitrogen/kg · d (17% of total calories, Aminosyn II; Abbott, North Chicago, IL), and 30% of nonprotein calories from fat (Liposon III; Abbott). The remaining calories were provided as dextrose (58.1% of total calories) (Abbott). The amount of administered calories was estimated based on the measured energy expenditure from our previous studies.

The animals that received only TPN comprised the control group (control). The other 4 groups received TPN plus endotoxin. Endotoxin was administered at 1 mg/d and mixed with TPN solution. Although endotoxin may be bound by lipids and lose some of its activity, our previous studies showed that this dose of endotoxin induces a chronic catabolic state. Insulin (5 mU/kg · h) or IGF-I (20 μg/kg · h) were also mixed with TPN. A total of 5 groups were included: (1) control, (2) endotoxin + saline, (3) endotoxin + IGF-I 20 μg/kg · d (IGF-I), (3) endotoxin + insulin 5 mU/kg · h (insulin), and (4) endotoxin + a combination of IGF-I 20 μg/kg · h and insulin 5 mU/kg · h (IGF/insulin).

Nutrient intake was recorded every day. Urine samples were collected daily for determination of total nitrogen. For the last 4 hours of feeding, all animals were transferred to plastic metabolic cages for measurement of protein and glucose turnover using [1-^{14}C]leucine and high-performance liquid chromatography (HPLC)-purified [3-^{3}H]glucose.

The [1-^{14}C]leucine and [3-^{3}H]glucose were mixed with TPN solution and constantly infused into the animals for 4 hours at a rate of 1.2 and 5 μCi/h, respectively, to reach isotopic steady state using a Harvard Pump (Harvard Apparatus, Natick, MA). During the isotope infusion period, CO_2 production, O_2 consumption, the respiratory quotient, and $^{14}CO_2$ specific activity in expired breath were determined at 30-min intervals.

At the end of the infusion, all animals were decapitated and the blood was collected for determination of plasma glucose, IGF-I, insulin, leptin, and leucine and glucose specific activities. Portions of the liver and rectus abdominis muscle representing muscle with mixed fiber types were removed and weighed for determination of leucine kinetics. All samples, including plasma and tissues, were stored at −20°C until analysis. Mortality prior to termination of the experiment was recorded in each group. Since not all animals in the mortality study received isotopes, the number of animals in which protein and glucose kinetics were measured is not the same as for the mortality study in each group.

The experiment was approved by the Animal Care Committee of Beth Israel Deaconess Medical Center, which follows the guidelines established for the care and use of laboratory animals of the Institute of Laboratory Animal Resources, National Research Council.

Reagents

The regular insulin (Eli Lilly & Co, Indianapolis, IN) was of beef and pork origin. Recombinant human IGF-I was a gift from Genentech (South San Francisco, CA). Lipopolysaccharide (*E coli* 026:B6) was obtained from DIFCO Laboratories (Detroit, MI).

Analytical Procedures

Plasma glucose was determined using a Beckman (Fullerton, CA) glucose analyzer (glucose oxidase method). The plasma leptin level was measured using a murine leptin kit (Linco Research, St. Charles, MO). Commercial human radioimmunoassay kits were used for determination of plasma insulin using porcine insulin standards (Ventrex Laboratories, Portland, ME). IGF-I radioimmunoassay kits (Nichols Institute, San Juan Capistrano, CA) were used to measure total IGF-I in acid-ethanol–extracted plasma samples using DNA-recombinant IGF-I standards.

The specific activities of [1-^{14}C]leucine in plasma and tissues were measured as previously described.[11,12] Plasma was separated and deproteinized with 30% sulfosalicylic acid (SSA). Tissues were homogenized in 10% SSA. The supernatants of both plasma and tissues were analyzed for leucine content by HPLC. Total radioactivity in these supernatants was measured by scintillation spectroscopy (Beckman Instruments) after removal of [α-^{14}C]ketoisocaproate with H_2O_2.

The specific activity of leucine in the protein-bound fraction in tissues was determined by analyzing samples of the tissue homogenates precipitated with SSA after drying and solubilization in 0.5 N quaternary ammonium hydroxide (Beckman BTS-450; Beckman Instruments) using scintillation spectroscopy (Beckman Instruments). The leucine content of the tissue samples was estimated from the nitrogen content analyzed by a micro-Kjeldahl method and the percent leucine content of the various tissue proteins.[8] Urine nitrogen was determined by a micro-Kjeldahl method. Glucose specific activity in plasma was determined as previously described.[13]

The specific activity of CO_2 was determined by trapping the expired breath in vials containing a mixture of Hyamine hydroxide (Packard Instruments, Downers Grove, IL) in absolute alcohol and 0.1% phenolphthalein as an indicator. These vials were then analyzed for radioactivity with a Beckman LS-6000 liquid scintillation spectrometer using Betafluor (National Diagnostic, Manville, NJ) as a scintillation fluid.

Calculations

The rate of plasma leucine flux was calculated from the dilution of label at isotopic steady state as previously described,[11,12] flux = I/Sp_{max}, where I is the infusion rate of [^{14}C]leucine and Sp is the specific activity of circulating leucine in mixed blood expressed as dpm per micromole. On the basis of the circulating leucine flux, the major component of whole-body leucine metabolism can be further evaluated according to the equation, flux = intake + breakdown = synthesis + oxidation, where intake is the dietary leucine intake, breakdown is the contribution from body protein breakdown, synthesis is the rate of utilization of plasma leucine in protein synthesis, and oxidation is the leucine oxidation rate.

The rate of plasma leucine oxidation was calculated from the product of plasma flux and the percentage of infused tracer appearing in breath. The latter was measured according to the equation, oxidation = $\dot{V}CO_2 \times SA[^{14}CO_2]/0.8 \times 1$, where $\dot{V}CO_2$ and $SA[^{14}CO_2]$ are the rate of CO_2 production and its steady-state specific activity in breath, respectively, measured by indirect calorimetry and analysis of expired $^{14}CO_2$ in Hyamine hydroxide, and I is the rate of infusion of [^{14}C]leucine. An estimated CO_2 retention of 0.8 was used.[14]

The absolute rate of leucine incorporation into liver and muscle (Ts) was calculated by multiplying the FSR by the leucine mass of the tissue under consideration (μmol/g · h), Ts = FSR × leucine mass, where FSR is the fractional protein synthesis rate and leucine mass is the leucine content in the dry tissue under consideration. The FSR is derived from the following relationship between leucine specific activities in protein (acid-insoluble homogenate fraction, Sb) and in the free amino acid precursor pool (acid-soluble homogenate fraction, Si).

$$\frac{Sb}{Si} = \frac{\lambda i}{(\lambda i - Ks)} \cdot \frac{(1 - e^{-Kst})}{(1 - e^{-\lambda it})} - \frac{Ks}{(\lambda i - Ks)}$$

where t is the time of tracer infusion, λ_i is the rate of appearance of tracer in the precursor pool, and Ks is the FSR. The λ_i in the liver and muscle was obtained from previous studies.[14]

The rate of breakdown for the protein mass (Tb) was calculated by the equation previously reported by this laboratory,[11,12] Tb = q × I × (Sp − Si)/Si × Sp, where q is the fraction of infused tracer distributed to the tissue and I is the rate of tracer isotope infusion; Si and Sp are previously defined. The Ts/Tb ratio was calculated as an anabolic index. A higher ratio indicates more leucine (protein) remaining in the tissue.

Nitrogen balance was calculated from the difference between nitrogen intake and urinary nitrogen output.

The rate of glucose appearance (flux) was calculated using the infusion rate of ^{3}H-labeled tracer (I) and steady-state plasma 3-^{3}H-glucose specific activity, $flux_{glucose}$ = I/plasma [^{3}H]glucose specific activity. The rate of glucose clearance in plasma was calculated using the flux divided by the plasma glucose concentration, glucose clearance rate = $flux_{glucose}$/glucose $concentration_{plasma}$.

Statistical Analysis

Statistical analysis of the data for different groups was performed with 1-way ANOVA using the SYSTAT statistical software program (Systat, Evanston, IL). Comparisons among groups were made by the least-significant difference (LSD) test when ANOVA was found to be significant at the 95% confidence level. Differences in mortality were compared by chi-square analysis. The results are presented as the mean ± SE.

RESULTS

In TPN-infused rats, plasma glucose and insulin were 111 ± 5 mg/dL and 93 ± 14 μU/mL in normal controls, respectively. However, both values were significantly elevated (126 ± 4 mg/dL and 202 ± 18 μU/mL) in endotoxemic rats (endotoxin group, $P < .05$ and $P < .005$; Table 1). Therefore, the ratio of glucose to insulin, as an index of insulin sensitivity, was significantly lower in endotoxemic rats compared with the controls. There were no significant differences in the plasma IGF-I concentration between the controls and the endotoxin-only group during TPN feeding.

For endotoxemic rats, coinfusion of TPN with IGF-I or insulin reduced plasma glucose to the level found in the controls. Administration of IGF-I either alone or in combination with insulin significantly decreased plasma insulin but significantly increased IGF-I as compared with the other groups. The ratio of glucose to insulin was higher in both IGF-I–treated groups.

Plasma leptin levels were significantly higher in all endotoxemic groups compared with the controls (Table 1). However, there was no correlation between plasma levels of leptin and insulin among the 4 endotoxemic groups.

Energy expenditure was significantly higher in the endotoxemic group compared with the control, indicating a higher metabolic rate. However, administration of IGF-I or insulin did not alter the changes in energy expenditure induced by endotoxin. The respiratory quotient was not different among the groups.

Glucose intake, plasma glucose flux, and glucose clearance in plasma were not significantly different among the groups. Whole-body leucine kinetics, including plasma leucine flux, synthesis, breakdown, and oxidation, and the rate of plasma flux oxidized also were not significantly different among the groups. However, endotoxin infusion significantly increased the liver weight and protein content in the liver compared with the controls. Although there were no significant differences in the FSR and the rates of protein synthesis and protein breakdown in the liver among the groups, the FSRs ($P = .06$ by ANOVA) were marginally higher in all endotoxemic groups compared with controls. In the muscle, endotoxin infusion significantly decreased the Ts/Tb ratio, an anabolic index, suggesting that less protein was preserved in this tissue even with TPN feeding. However, with IGF-I and TPN coinfusion, this ratio was significantly increased, with a further significant increment with the administration of insulin either alone or in combination with IGF-I (Table 2).

After 3 days of TPN feeding, normal control animals maintained their body weight. In contrast, endotoxemic animals had significantly increased body weight in the range from 7 to 14 g (data not shown). There were no significant differences among the 4 endotoxemic groups.

Mortality in each group is shown in Table 3. There were no deaths (0 of 11) in the normal control animals. The mortality in the endotoxin group with saline treatment was 53% (8 of 15), significantly higher than the rate found for the coinfusion of insulin or the combination of IGF-I and insulin, where the mortality of endotoxemic animals was significantly reduced to 7% (1 of 14) and 15% (2 of 13), respectively.

DISCUSSION

During TPN feeding, endotoxin significantly decreased the amount of leucine (protein) maintained in the muscle tissue as compared with normal controls, indicated by the lower Ts/Tb ratio in this tissue. Muscle protein makes a significant contribution to whole-body protein metabolism.[15] Indeed, the reduced leucine in muscle tissue led to a significant reduction in body nitrogen retention (38% less) as compared with the control (0.71 ± 0.06 *v* 1.13 ± 0.07 g nitrogen/kg body weight on the last day of feeding, $P < .05$; data not shown), although the liver increased in size and in protein content. Since the normal control and endotoxemic animals received the same amount of calories and protein through TPN, these results suggest that

Table 1. Plasma Glucose, Insulin, Leptin, and IGF-I

Parameter	Controls (n = 8)	Endotoxin Groups			
		Endotoxin (n = 15)	IGF-I (n = 10)	Insulin (n = 12)	IGF/Insulin (n = 11)
Glucose (mg/dL)*	111 ± 5	126 ± 4‡	114 ± 3	113 ± 4	107 ± 5
Insulin (μU/mL)†	93 ± 14	202 ± 19§	141 ± 19	207 ± 20§	143 ± 22
Glucose/insulin*	1.3 ± 0.2	0.7 ± 0.1‖	0.9 ± 0.2	0.6 ± 0.1‖	0.9 ± 0.1
Leptin (ng/mL)†	1.2 ± 0.1‡	2.0 ± 0.2	2.0 ± 0.2	2.5 ± 0.3	1.8 ± 0.2
IGF-I (ng/mL)*	625.9 ± 39.0	683.1 ± 22.8	788.7 ± 27.5¶	693.6 ± 16.5	767.8 ± 47.0¶

NOTE. Results are the mean ± SE.

*$P < .05$, †$P < .005$ by 1-way ANOVA.

‡$P < .05$ *v* all.

§$P < .005$ *v* controls, IGF-I, and IGF/insulin.

‖$P < .05$ *v* controls.

¶$P < .01$ *v* controls, endotoxin, and insulin (all by LSD test).

Table 2. Estimates of Muscle Protein Kinetics

Parameter	Controls (n = 8)	Endotoxin Groups			
		Endotoxin (n = 15)	IGF-I (n = 10)	Insulin (n = 12)	IGF/Insulin (n = 11)
Protein content (%)	18.0 ± 1.6	17.3 ± 1.4	17.3 ± 1.0	18.9 ± 1.3	18.0 ± 0.9
FSR (%/d)	6.3 ± 1.0	5.1 ± 0.4	5.1 ± 0.6	5.9 ± 0.5	5.4 ± 0.7
Ts (μmol/g · h)	0.32 ± 0.07	0.20 ± 0.02	0.22 ± 0.03	0.28 ± 0.04	0.27 ± 0.05
Tb (μmol/g · h)	0.44 ± 0.08	0.55 ± 0.06	0.53 ± 0.01	0.43 ± 0.04	0.41 ± 0.05
Ts/Tb*	0.73 ± 0.01	0.36 ± 0.01†	0.42 ± 0.02‡§	0.65 ± 0.02	0.66 ± 0.01

NOTE. Results are the mean ± SE.

*$P < .05$ by 1-way ANOVA.

†$P < .05$ *v* all, ‡$P < .05$ *v* controls, insulin, and IGF/insulin, §$P = .05$ *v* endotoxin by LSD test.

non-nutritional factors that develop during systemic inflammation play an important role in regulating and preserving body protein mass.

In the current study, there were a number of significant hormonal changes during endotoxin infusion. Plasma levels of glucose and insulin were significantly elevated in endotoxemic rats compared with normal controls. Insulin sensitivity was also significantly lower in endotoxemic animals. In contrast to some reports, the current study did not find a reduction in plasma IGF-I with endotoxin infusion.[16-18] Differences in the method of administration of endotoxin may account for these inconsistencies. In the present study, endotoxin was continuously infused into the animals at a rate of 1 mg/kg · d for 3 days at a dose lethal to approximately 20% of animals at 24 hours. In a previous study,[19] endotoxin was bolus-injected at 1 mg/kg. Therefore, the administered dose of endotoxin per unit time in the present study was dramatically less, but the total amount and duration of endotoxin administration were substantially greater. As a second consideration, tachyphylaxis to endotoxin effects may have developed after 3 days of endotoxin infusion in the current study. Finally, the animals in the present study received nutritional support at 220 kcal/kg · d with ample provision of essential nutrients, whereas the animals were fasted overnight in the earlier study.

For the endotoxemic animals, administration of either insulin or IGF-I significantly decreased plasma glucose to a level found in normal controls. Moreover, IGF-I administration significantly increased the plasma IGF-I concentration and clearly suppressed insulin secretion, as reflected by the plasma insulin level. Many studies have demonstrated a dose-dependent increase in insulin and IGF-I concentrations following their administration.[20,21] However, insulin administration in the current study did not further increase the plasma insulin concentration when compared with the endotoxin group without hormone treatment. The failure to increase plasma insulin suggests a maximal response of insulin secretion to TPN feeding for 3 days in these animals, and thus exogenous insulin administration may lead to a compensatory decrease in endogenous secretion.

Consistent with previous findings,[21] leptin levels were significantly higher in all endotoxin groups, which may be associated with the hyperinsulinemia induced by endotoxin infusion. It has been suggested that insulin can regulate leptin secretion. In healthy individuals with normal body weight, exogenous hyperinsulinemia increases serum leptin.[22] However, no correlation was observed between insulin and leptin among these 4 endotoxemic groups, perhaps due to the greater impact of endotoxin on leptin metabolism.[23]

Insulin and IGF-I did not show significant stimulatory effects on protein synthesis and protein breakdown at the whole-body level. There was an increase in the Ts/Tb ratio only in muscle tissue, indicating that these hormones can preserve protein in this important tissue during TPN feeding in an endotoxemic condition. Moreover, neither hormone had an impact on glucose utilization and glucose production, although the plasma glucose concentration that was elevated by endotoxin was restored to control levels. It is possible that with TPN feeding for 3 days, the considerable anabolic effects of nutrients achieved a near-maximal stimulation of protein synthesis and glucose utilization and/or suppression of protein breakdown, making it difficult to detect incremental responses to or differential effects of IGF-I and insulin. However, the present results may be explained by the results reported in another study,[24] that the ability of insulin or IGF-I to limit protein degradation in septic rats was severely blunted 48 hours after infection and the effect of insulin or IGF-I to inhibit proteolysis was more pronounced on day 6 postinfection than on day 2 postinfection.

No additive effect of these two hormones was observed in any measured parameter. This may be attributed, in part, to the interaction of IGF-I and insulin metabolism and the cross-reactivity of the ligands with the insulin and IGF-I receptors. It has been reported and confirmed in this study that IGF-I suppresses insulin secretion, which would reduce insulin's anabolic action and the net benefit of IGF-I given alone or in combination with insulin. IGF-I administration also leads to a reduction of IGF-I binding protein-3 (IGFBP-3) and an increase of IGFBP-1 and IGFBP-2.[25] These latter effects are known to reduce the anabolic effect of IGF-I. An inverse correlation between free IGF-I and IGFBP-1 is also observed,[26] with free IGF-I being the principal anabolic stimulus. Thus, the anabolic actions of IGF-I on protein metabolism can be limited even though total IGF-I levels are increased after administration of IGF-I. Therefore, IGF-I administration reduces the anabolic contribution of insulin, and insulin administration reduces the anabolic contribution of IGF-I, since in none of the 3 hormone groups were insulin and IGF-I elevated simultaneously. Only when insulin was provided was mortality significantly reduced. The improvement in mortality is more likely to involve specific

Table 3. Mortality in the Different Groups

	Controls	Endotoxin Groups			
		Endotoxin	IGF-I	Insulin	IGF/Insulin
Mortality (%)	0	53	33	7	15
Death/survival (n)	0/11	8/15*	4/12	1/14	2/13

*$P < .05$, endotoxin *v* controls, insulin, and IGF/insulin.

effects of insulin on cardiovascular or cardiorespiratory systems.[27] This effect may have important clinical implications, since virtually all therapies that improve the response to lethal endotoxin doses require pretreatment before endotoxin administration.[28-30] Certainly, this will require substantial further experimentation to assess the reproducibility and potential mechanisms of this finding.

Finally, it is well known that administration of endotoxin can induce high mortality or early recovery. Moreover, prolonged or repeated administration leads to endotoxin tolerance, which is also observed with continuous infusion of endotoxin. In the present study, continuous infusion of endotoxin for 3 days produced a catabolic condition. Moreover, continuous provision of endotoxin can be a model of the clinical situation in man where a systemic inflammatory response is continuously present but blood cultures are often not positive for organisms. In about half of the cases of clinical sepsis, positive blood cultures are not found.

In conclusion, when the dosages of insulin and IGF-I were matched to maintain normal plasma levels of leucine and glucose during TPN, both hormones had effects on preserving protein in muscle tissue in endotoxemic rats. Insulin appeared to have greater potency for this effect. However, the combination of these two anabolic hormones did not provide additive effects, presumably because each hormone reduced the secretion and efficiency of the other.

REFERENCES

1. Wilmore DW: Catabolic illness. N Engl J Med 325:695-702, 1991
2. Shaw JH, Wildbore M, Wolf RR: Whole body protein kinetics in severe septic patients. Ann Surg 205:288-294, 1987
3. Streat SJ, Beddoe AH, Hill GL: Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma 27:262-266, 1987
4. Loder PB, Smith RC, Kee AJ, et al: What rate of infusion of intravenous nutrition solution is required to stimulate uptake of amino acid by peripheral tissues in depleted patients? Ann Surg 211:360-368, 1990
5. Kwoun MO, Ling PR, Lydon E, et al: Immunologic effects of acute hyperglycemia in non-diabetic rats. JPEN 21:91-95, 1997
6. Yang H, Grahn M, Schalch DS, et al: Anabolic effects of IGF-I coinfused with total parenteral nutrition in dexamethasone-treated rats. Am J Physiol 266:E690-E698, 1994
7. Lo H-C, Hinton PS, Yang H, et al: Insulin-like growth factor-I but not growth hormone attenuates dexamethasone-induced catabolism in parenterally fed rats. JPEN 20:171-177, 1996
8. Moses AC, Young SC, Morrow LA, et al: Recombinant human insulin-like growth factor I increases insulin sensitivity and improves glycemic control in type II diabetes. Diabetes 45:91-100, 1996
9. Fryburg DA: Insulin-like growth factor I exerts growth hormone and insulin-like actions on human muscle protein metabolism. Am J Physiol 267:E331-E336, 1994
10. Ling PR, Gollaher C, Colon E, et al: Effects of recombinant human insulin-like growth factor (IGF-I) on energy and protein metabolism in fed and fasted rats. Am J Clin Nutr 61:116-120, 1995
11. Flores E, Bistrian BR, Pomposelli JJ, et al: Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. J Clin Invest 83:1614-1622, 1989
12. Ling PR, Schwartz JH, Jeevanandam J, et al: Mechanisms of host wasting induced by administration of cytokines in rats. Am J Physiol 272:E333-E339, 1997
13. Ling PR, Sierra P, Qu Z, et al: Insulin-like growth factor-I improves glucose utilization in tumor necrosis factor–treated rats under hyperinsulinemic-euglycemic conditions. Metabolism 46:1052-1058, 1997
14. Moldawer LL, Kawamura I, Bistrian BR, et al: The contribution of phenylalanine to tyrosine metabolism in vivo. Studies in the post-absorptive and phenylalanine-loaded rat. Biochem J 210:811-817, 1983
15. Long CL, Birkhahn RH, Geiger JW: Contribution of skeletal muscle protein in elevated rates of whole body protein catabolism in trauma patients. Am J Clin Nutr 34:1087-1093, 1981
16. Faggioni R, Fuller J, Moser A, et al: LPS-induced anorexia in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice. Am J Physiol 273:R181-R186, 1997
17. Elsasser TH, Gaperna TJ, Rumsey TS: Endotoxin administration decreases plasma insulin-like growth factor (IGF-I) and IGF-binding protein 2 in Angus × Hereford steers independent of changes in nutritional intake. J Endocrinol 144:109-117, 1995
18. Lang CH, Pollard V, Fan J, et al: Acute alterations in growth hormone–insulin-like growth factor axis in humans injected with endotoxin. Am J Physiol 273:R371-R378, 1997
19. Fan J, Char D, Kolasa AJ, et al: Alterations in hepatic production and peripheral clearance of IGF-I after endotoxin. Am J Physiol 269:E33-E42, 1995
20. Boulware SD, Tamborlane WV, Rennert NJ, et al: Comparison of the metabolic effects of recombinant human insulin-like growth factor-I and insulin. Dose-response relationship in healthy young and middle-aged adults. J Clin Invest 93:1131-1139, 1994
21. Grunfeld C, Zhao C, Fuller J, et al: Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. J Clin Invest 97:2152-2157, 1996
22. Boden G, Chen X, Kolaczynski JW, et al: Effects of prolonged hyperinsulinemia on serum leptin in normal human subjects. J Clin Invest 100:1107-1113, 1997
23. Sarraf P, Frederich RC, Turner EG, et al: Multiple cytokines and acute inflammation raise mouse leptin levels: Potential role in inflammatory anorexia. J Exp Med 185:171-175, 1997
24. Vary TC, Dardevel D, Grizard J, et al: Differential regulation of skeletal muscle protein turnover by insulin and IGF-I after bacteremia. Am J Physiol 275:E584-E593, 1998
25. Quin JD, Checkley A, Gallagher A, et al: Response of insulin-like growth factor (IGF)-binding protein-I (IGFBP-I) and IGFBP-3 to IGF-I treatment in severe insulin resistance. J Endocrinol 141:177-182, 1994
26. Young SC, Clemmons DR: Changes in insulin-like growth factor (IGF)-binding proteins after IGF-I injection in non insulin-dependent diabetes. J Clin Endocrinol Metab 78:609-614, 1994
27. Lazar HL, Philippides G, Fitzgerald C, et al: Glucose-insulin-potassium solutions enhance recovery after urgent coronary artery bypass grafting. J Thorac Cardiovasc Surg 113:354-362, 1997
28. Mascioli E, Iwasa Y, Trimbo S, et al: Endotoxin challenge after menhaden oil diet. Effects on survival of guinea pigs. Am J Clin Nutr 49:277-282, 1989
29. Wise WE, Cook JA, Eller T, et al: Ibuprofen improves survival from endotoxin shock in the rat. J Pharmacol Exp Ther 215:160-164, 1980
30. Tracey K, Fong Y, Hesse D, et al: Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 330:662-664, 1987