Growth Hormone Modulates Amino Acid Oxidation in the Surgical Patient: Leucine Kinetics During the Fasted and Fed State Using Moderate Nitrogenous and Caloric Diet and Recombinant Human Growth Hormone

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Twelve patients (aged 70 ± 9 years) who were scheduled for resection of rectosigmoid colon adenocarcinoma but were otherwise healthy were randomly allocated after surgery to receive either peripheral parenteral nutrition alone ([PPN] n = 6) or in combination with recombinant human growth hormone (rGH) at a daily dose of 0.15 U · kg^{-1} · d^{-1} (PPN + rGH, n = 6). The daily nutritional regimen was 0.1 g nitrogen · kg^{-1} · d^{-1} and 20 kcal · kg^{-1} · d^{-1} (nonprotein energy was supplied as 60% lipid and 40% carbohydrate), and it was maintained for 6 days before and 6 days after surgery. Protein kinetics were studied in all 12 patients during the fasted and fed states before and 6 days after surgery using an 8-hour ^{13}C-leucine tracer infusion. Daily urinary nitrogen, gaseous exchange, and plasma insulin, growth hormone, and insulin-like growth factor-I (IGF-I) were determined before and after surgery. Surgery was responsible for significant increases in postabsorptive whole-body protein flux and synthesis and leucine oxidation ($P < .01$). Supplementation of PPN with rGH contributed to a significant attenuation of the postoperative increase in leucine oxidation ($P = .02$), with a significant increase in whole-body protein synthesis ($P = .02$) and no effect on protein breakdown ($P = .40$). During the fed state, leucine oxidation increased significantly ($P = .005$), with the greatest change occurring in the PPN group. Feeding was associated with a significant decrease in whole-body protein breakdown before and after surgery in both groups ($P = .001$). Postoperative urinary nitrogen excretion was lower but was not statistically significant in the PPN + rGH group compared with the PPN group. There was a significant increase in oxygen consumption ($\dot{V}o_2$) and carbon dioxide production ($\dot{V}co_2$) as a result of feeding and surgery ($P < .01$). Supplementation with rGH caused a decrease in the respiratory quotient (RQ) ($P = .04$), particularly after surgery, indicating a direct effect of rGH on fatty acid oxidation. Circulating plasma insulin increased significantly in both groups with feeding and rGH supplementation ($P < .05$). This was enhanced after surgery, particularly in the rGH group ($P < .05$). Plasma growth hormone decreased after surgery in the PPN group ($P < .05$), but did not change as a result of feeding. The circulating levels increased in the PPN + rGH group following subcutaneous administration before or after surgery. Plasma IGF-I decreased after surgery in the PPN group ($P < .05$), and no changes occurred in the PPN + rGH group with feeding. The present findings suggest a distinct positive effect of rGH on protein synthesis in catabolic patients receiving a moderate intake of nitrogen and calories. This is achieved by modulation of amino acid oxidation. The acute effect of intravenous (IV) nutrients on protein metabolism during the catabolic phase of surgical stress caused a direct decrease in protein breakdown with no effect on protein synthesis.

TRAUMA resulting from major surgery initiates a complex series of endocrine and neuroendocrine reactions that result in a characteristic metabolic response.[1] One prominent feature is negative nitrogen balance, wherein postoperative urea production is increased and urinary excretion of nitrogen exceeds intake. In severely ill or metabolically compromised patients, this catabolic state may increase the susceptibility to infection and poor wound healing, and therefore prolong recovery. The features of negative nitrogen balance are increased whole-body protein flux as a result of increased catabolism and increased synthesis.[2-4]

The anabolic effects of recombinant human growth hormone (rGH) on protein metabolism have long been established in volunteers,[5] surgical and critically ill patients.[6-9] These are due to stimulation of the synthesis of insulin-like growth factor-I (IGF-I),[10] which may act as both an endocrine and a paracrine hormone. Positive nitrogen balance has been shown to occur in surgical patients when a hypocaloric diet (800 to 1,200 kcal) with adequate nitrogen was supplied and supplemented with rGH.[11]

Administration of growth hormone to stressed patients (major surgery, burns, or sepsis) in negative nitrogen balance, with the goal of improving the nitrogen balance, has produced conflicting results. Jiang et al[7] and Mjaaland et al[12] demonstrated improved nitrogen balance after administering growth hormone to surgically stressed patients, as did Liljedahl et al,[13] in burn patients. Several groups have been unable to demonstrate an improvement in the nitrogen status of septic patients.[14-16]

The periodic nature of human nutrition, with cycles of fasting and feeding, results in losses and gains of body proteins in subjects in nitrogen balance.[17] The response of protein metabolism to dietary intake in adult man has received great attention, but the picture is far from clear. Measurements of whole-body protein metabolism in volunteers during the fed state have given rise to differing conclusions that suggest either an increased rate of protein synthesis or a decreased body protein breakdown.[18-21]

Studies on protein metabolism using stable-isotope methodology in surgically stressed patients receiving nutritional support have been conducted in the postabsorptive state,[3,4] and the results indicate an increase in all aspects of whole-body protein metabolism. However, there is a need to clarify to what extent nutrients are used during the catabolic phase of injury.

Therefore, it is imperative that the effect of nutritional support on whole-body protein turnover and amino acid oxida-

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tion be investigated in the fed state in addition to the more usual postabsorptive state. The present study was conducted using tightly controlled perioperative intake of nitrogen and calories, and was designed to assess (1) the effect of rGH supplementation on protein synthesis and leucine oxidation, and (2) the acute effect of intravenous (IV) feeding on postsurgical protein breakdown.

SUBJECTS AND METHODS

Twelve patients scheduled to undergo elective resection of localized nonmetastatic adenocarcinoma of the rectosigmoid colon were studied. None of the patients suffered from malnutrition or recent weight loss, and all were otherwise healthy. Patients with anemia, diabetes, morbid obesity, or severe cardiovascular disorders were excluded. The study was approved by the Ethics Committee of Northwick Park Hospital, and all patients provided written, informed consent.

Nutrition

A nutrition regimen based on 0.1 g nitrogen $\cdot kg^{-1} \cdot d^{-1}$ and 20 kcal $\cdot kg^{-1} \cdot d^{-1}$ was used for the study. Nonprotein calories were 60% lipid and 40% carbohydrate. This oral intake was started 6 days before surgery under dietetic supervision, and was then changed to peripheral parenteral nutrition ([PPN] 500 mL Vamin 14, 1 L Intralipid 10%, and 1 L dextrose 10%; Kabi Pharmacia) 2 days before surgery and continued for 6 days afterward.

On the day of surgery, patients were randomly allocated to two groups: PPN (control group, n = 6), and PPN + rGH (treatment groups, n = 6), who received rGH in addition to peripheral IV nutrition (PPN).

In the PPN + rGH group, rGH (Genotrophin; Kabi-Pharmacia, Sweden) was administered subcutaneously (0.15 U $\cdot kg^{-1} \cdot d^{-1}$) at 12:00 noon on the day of surgery and for 5 days postoperatively. In the PPN group, an equivalent volume of 0.9% NaCl was administered at the same time. Neither the patient nor the investigators were aware of the treatment received.

Anesthesia and Surgical Care

General anesthesia was achieved with thiopentone, vecuronium, enflurane, and nitrous oxide in oxygen. Postoperative pain relief was achieved and maintained for 3 to 4 days with a subcutaneous infusion of papaveretum 3 to 5 mg $\cdot h^{-1}$. The duration of surgery ranged from 160 to 205 minutes. Mean blood loss was 678 mL (range, 549 to 896) and 750 mL (range, 575 to 995) for the PPN and PPN + rGH groups, respectively, and this was replaced, if needed, with 1 or 2 U autologous blood. Hartmann's solution (4 to 6 mL $\cdot kg^{-1} \cdot h^{-1}$) was infused IV during surgery.

Protein Kinetics

The experimental protocol is shown in Fig 1, and the leucine kinetics study during the fasted and fed states is presented in Fig 2.

Protein metabolism was studied using steady-state leucine kinetics before and 6 days after surgery. All patients were fasted for 12 hours before commencement of the isotope studies, and all studies were started at 8:00 AM. A superficial vein in the dorsum of the hand was cannulated to provide access for infusion of L-[1-^{13}C]leucine. Blood was sampled from a cannula placed in the contralateral hand vein. L-[1-^{13}C]leucine (99% ^{13}C) and 99% ^{13}C-sodium bicarbonate ($NaH^{13}CO_3$) were purchased from Cambridge Isotope Laboratories (Cambridge, MA).

Blood and air samples were collected before the infusion to measure basal ^{13}C enrichment, after which priming doses of $NaH^{13}CO_3$ 0.08 mg $\cdot kg^{-1}$ and L-[1-^{13}C]leucine 0.5 mg $\cdot kg^{-1}$ were administered. The continuous infusion of labeled leucine was started immediately and continued throughout the study period (8 hours). In the fasted state (4 hours) and 2 hours after the start of isotope infusion, when the tracer was assumed from previous studies to have reached isotopic steady state, venous blood and expired-air samples were collected at intervals of 15 minutes.

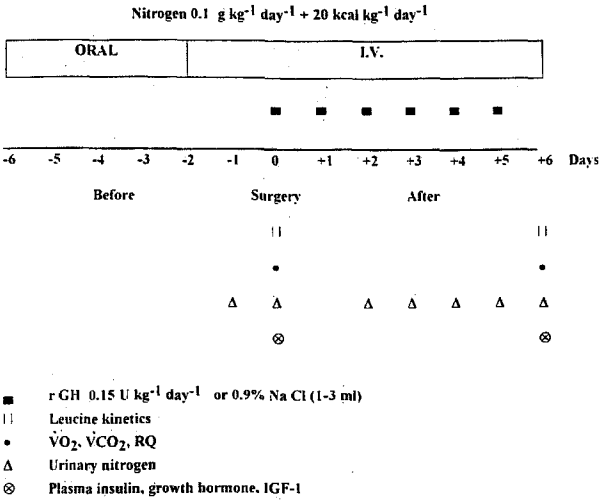

Fig 1. Study protocol before, during, and after surgery.

The leucine infusion was then continued for another 4 hours (fed state), during which time PPN was administered. A dose of rGH or an equivalent volume of 0.9% NaCl was administered subcutaneously at the beginning of the fed state in the PPN + rGH group. The time of administration of rGH during the study corresponded to that of the daily postoperative injection.

During the fed state, crystallized beet sugar (10% Dextrose anhydrous; Avebe, Foxhol, Holland) was used for preparation of the PPN infusion. This solution was prepared by the local pharmacy under sterile conditions and shown to be pyrogen-free. The low ^{13}C content of this solution had been assessed previously by monitoring the lack of significant perturbation of $^{13}CO_2$ enrichment in expired air when the

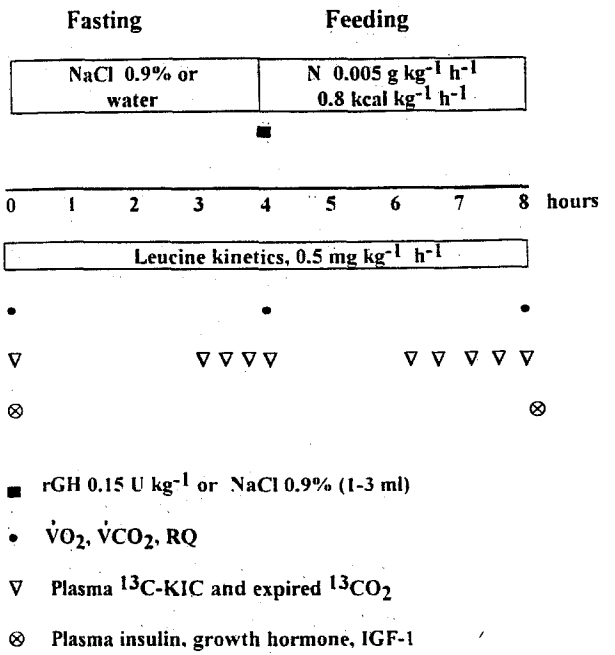

Fig 2. Fasted and fed states before and after surgery.

dextrose was infused into three control subjects at the rate of and for a duration similar to that used in the study. A solution containing a mixture of dextrose, amino acids, and lipids administered IV had been found not to perturb baseline $^{13}CO_2$ enrichment in expired air.

The rate of infusion of the solution was determined by the body weight and hourly requirements of the patient. The amount of leucine administered in the PPN solution during the fed state was calculated.

Venous blood and expired-air samples were taken at 15-minute intervals for the last 2 hours of the kinetic study. All blood samples were centrifuged immediately at 4°C, and the plasma was stored at −70°C until required for analysis. Plasma α-[^{13}C]ketoisocaproate (α-KIC) enrichment was determined by electron-impact selected-ion gas chromatography/mass spectrometry using ketovaleric acid as an internal standard. $^{13}CO_2$ enrichment in expired breath was determined on the day of study by isotope ratio mass spectrometry.[22] Plateau enrichment for both plasma α-KIC and expired carbon dioxide was considered to have been established provided the coefficient of variation was less than 5% during the steady state (2 to 4 and 6 to 8 hours).

Whole-body leucine kinetics were calculated using a two-pool stochastic model applied during the steady-state conditions of each study.[23] Plasma enrichment of α-[^{13}C]KIC was used as the basis for calculating both flux and oxidation of leucine.[24] In the calculation of oxidation, factors of 0.75 for the fasting state and 0.92 for the fed state were used to account for the fraction of $^{13}CO_2$ released from leucine but retained in the bicarbonate pool of the body.[25] Whole-body protein breakdown in the fed state was calculated by subtracting only the exogenous leucine intake of the PPN solution over the 4-hour infusion from the measured flux.

Urinary Nitrogen

Twenty-four-hour urine collections were made 2 days before surgery and daily for 5 consecutive days afterward. The nitrogen content of urine samples was measured by chemiluminescence,[26] and 24-hour excretion of nitrogen was calculated.

Gaseous Exchange

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed over a 30-minute period during the L-[1-^{13}C]leucine studies both in the fasted and fed states before and after surgery. Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured, and the respiratory quotient (RQ) was calculated.

Plasma Hormones

Blood samples for determination of plasma insulin, growth hormone, and IGF-I were taken during studies of leucine kinetics before surgery and 6 days afterward. Plasma concentrations of insulin were measured by a sensitive and specific double-antibody radioimmunoassay (Amersham International, Amersham, Bucks, UK). Intraassay and interassay precisions at 8 μU · mL^{-1} were 5.6% and 8.3%, respectively. Plasma growth hormone level was measured using a solid-phase two-site immunoradiometric assay (Netria Laboratories, London, UK). The level of detection for the assay was 0.5 μU · mL^{-1}, and within-assay coefficients of variation were 5%, 2.4%, and 2.6% at 1.0, 45.5, and 86.5 μU · mL^{-1}, respectively. Between-assay coefficients of variation were 3.3%, 5.2%, and 5.5%. Serum IGF-I level was measured after acid-ethanol extraction of its binding proteins, using a polyclonal rabbit antiserum (R557A) raised against purified human IGF-I.[27] The level of detection of this assay was 0.5 μU · mL−1, and the interassay coefficients of variation were 9.0%, 4.5%, and 6.2% at analyte levels of 35.6, 10.9, and 3.7 μU · mL^{-1}, respectively, with an intraassay coefficient of variation of 4% at 10.9 μU · mL^{-1}.

Table 1. Leucine Kinetics (μmol · kg^{-1} · h^{-1}) of the Two Groups Before and After Surgery in the Fasted and Fed States (mean ± SD)

Leucine Kinetics	Before Surgery		After Surgery	
	Fasted	Fed	Fasted	Fed
Flux				
PPN	112 ± 9	118 ± 11	157 ± 20	149 ± 11
PPN + rGH	122 ± 13	122 ± 10	158 ± 18	159 ± 19
Oxidation				
PPN	21 ± 4	29 ± 5	41 ± 8	49 ± 8
PPN + rGH	20 ± 5	24 ± 5	31 ± 7	34 ± 7
Synthesis				
PPN	91 ± 8	89 ± 12	116 ± 20	100 ± 13
PPN + rGH	102 ± 12	98 ± 10	127 ± 11	124 ± 16
Breakdown				
PPN	112 ± 9	100 ± 12	157 ± 20	132 ± 11
PPN + rGH	122 ± 13	105 ± 11	158 ± 18	141 ± 19

Statistical Analysis

Results are expressed as the mean ± 1 SD. Paired and unpaired Student's *t* tests were used when appropriate for urinary nitrogen and plasma insulin, growth hormone, and IGF-I. The results of leucine kinetics and gaseous exchange were analyzed using ANOVA with three factors. The factors PPN (yes or no) and rGH (yes or no) and their interactions were assessed relative to the variation between subjects, and the factors surgery (yes or no) and feeding (fasted or fed state) and their interactions with PPN and rGH were assessed relative to the variation within subjects. Statistical significance was reached at *P* less than .05.

RESULTS

The age, body weight, and body mass index (mean ± 1 SD) for the PPN group were 71 ± 4 years, 65 ± 9 kg, and 21 ± 4 kg/m^2, respectively, and for the PPN + rGH group, 68 ± 6 years, 61 ± 7 kg, and 21 ± 3 kg/m^2, respectively. Demographic characteristics of the groups were comparable. There were four men and two women in the PPN group and three men and three women in the PPN + rGH group.

Leucine Kinetics

Changes in whole-body protein flux, oxidation, synthesis, and breakdown during the fasted and fed state and before and after surgery for both groups are presented in Table 1. *P* values from ANOVA for the factors rGH, surgery, and feeding and their interactions are presented in Table 2.

The leucine intake of PPN solution during the fed state (mean ± SD) before and after surgery was 17.2 ± 2.6 and 16.9 ± 2.5 μmol · kg^{-1} · h^{-1}, respectively, for the PPN group and 17.2 ± 1.4 and 17.3 ± 2.2 μmol · kg^{-1} · h^{-1} for the PPN +

Table 2. *P* Values for Leucine Kinetics (fasted and fed states)

Factor	Synthesis	Flux	Oxidation	Breakdown
rGH	.02*	.40	.02*	.40
RX	.06	.80	.005*	<.001*
OP	<.001*	<.001*	<.001*	<.001*
rGH × RX	.40	.90	.30	.90
rGH × OP	.30	.70	.02*	.70
RX × OP	.30	.40	.90	.30
rGH × RX × OP	.20	.20	.80	.20

Abbreviations: RX, feeding; OP, surgery.
*Statistically significant.

Table 3. Gaseous Exchange for the Two Groups Before and After Surgery in the Fasted and Fed States (mean ± SD)

Variable	Before Surgery		After Surgery	
	Fasted	Fed	Fasted	Fed
$\dot{V}O_2$ (mL)				
PPN	245 ± 63	294 ± 37	254 ± 73	336 ± 66
PPN + rGH	239 ± 51	298 ± 43	264 ± 66	320 ± 66
$\dot{V}CO_2$ (mL)				
PPN	192 ± 45	222 ± 23	205 ± 43	245 ± 51
PPN + rGH	180 ± 40	231 ± 27	199 ± 49	238 ± 38
RQ				
PPN	79 ± 5	76 ± 3	78 ± 5	73 ± 4
PPN + rGH	77 ± 7	78 ± 5	74 ± 4	74 ± 3

rGH group. Whole-body protein breakdown was calculated by subtracting leucine intake from leucine flux.

Effect of operation. Surgery resulted in a significant increase ($P < .001$) in whole-body protein flux, synthesis, and breakdown. Leucine oxidation increased after surgery by 100% in the PPN group and by 58% in the PPN + rGH group ($P < .001$). There were no significant interactions between rGH, surgery, and feeding.

Effect of rGH and feeding. Feeding and rGH administration had no significant independent effect on flux. Feeding resulted in a significant increase in oxidation ($P = .005$), and there was an interaction between rGH and surgery ($P = .002$). Supplementation with rGH resulted in a significant decrease in oxidation ($P = .002$). The increase in oxidation due to feeding and surgery was greatest in the group receiving PPN alone.

There were significant positive effects of rGH supplementation and surgery on protein synthesis ($P = .02$ and $P < .001$, respectively). Protein synthesis did not change ($P = .06$) with feeding. Supplementation with rGH had no effect on protein breakdown. This decreased significantly as a result of feeding ($P < .001$) either before or after surgery in both groups.

Urinary Nitrogen

Urinary excretion of nitrogen was comparable in both groups before surgery (0.21 ± 0.03 g · kg^{-1} · d^{-1} in the PPN group and 0.20 ± 0.04 g · kg^{-1} · d^{-1} in the PPN + rGH group). Cumulative postoperative nitrogen excretion was lower for the PPN + rGH group than for the PPN group (1.49 ± 0.31 *v* 1.90 ± 0.60 g · kg^{-1}, respectively), but this was not statistically significant.

Gaseous Exchange

Gaseous exchange for the two groups studied before and after surgery and in the fasted and fed states is presented in Table 3, and *P* values from ANOVA are shown in Table 4. A significant increase in $\dot{V}O_2$ and $\dot{V}CO_2$ ($P < .05$) was associated with feeding and surgery and their interaction. Supplementation with rGH had no effect on gaseous exchange, except for a decrease in RQ ($P = .04$) as a result of its interaction with surgery.

Plasma Hormones

Circulating levels of plasma insulin (Table 5) increased significantly in both groups with feeding ($P < .05$), and this was enhanced after surgery, especially in the PPN + rGH group ($P < .01$).

Table 4. *P* Values for Gaseous Exchange of the Two Groups Before and After Surgery (fasted and fed states)

Factor	$\dot{V}O_2$	$\dot{V}CO_2$	RQ
rGH	.20	.30	.10
RX	.04*	.02*	.1
OP	.03*	.04*	.03*
rGH × RX	.40	.30	.08
rGH × OP	.30	.30	.04*
RX × OP	.02*	.03*	.20
rGH × RX × OP	.10	.10	.20

NOTE. Abbreviations are as in Table 2.
*Statistically significant.

Circulating concentrations of plasma growth hormone decreased significantly after surgery in the fasted state in both groups ($P < .05$). In the PPN group, no significant effect of feeding was shown on plasma growth hormone, whereas it increased significantly in the PPN + rGH group both before and after surgery ($P < .01$).

Plasma IGF-I did not change in either group as a result of surgery during the fasted state. Although there was a lower circulating concentration of plasma IGF-I in the PPN group compared with the PPN + rGH group, feeding did not alter the IGF-I response in either group before or after surgery.

DISCUSSION

The present findings show an increased whole-body protein flux as part of the stress response to surgery, and this increase is the result of increased oxidation, synthesis, and breakdown. In the present investigation, a significant effect of rGH supplementation on protein synthesis was demonstrated together with an attenuated increase in leucine oxidation.

Abdominal surgery has been used by others to assess the effect of rGH supplementation during the postoperative period, since these patients are unable to receive nutrition. Although a positive effect on postoperative nitrogen balance has been shown, the results for whole-body protein turnover have not been consistent. Jiang et al[7] administered rGH for 7 days to a group of patients undergoing major abdominal surgery together with parenteral nutrition in a dose similar to that used in this study. In contrast to the present findings, they were able to demonstrate a significant decrease in nitrogen excretion during the postoperative period. They also measured nitrogen turnover

Table 5. Plasma Hormones of the Two Groups Before and After Surgery in the Fasted and Fed States (μU · mL^{-1}, mean ± SD)

Hormone	Before Surgery		6 Days After Surgery	
	Fasted	Fed	Fasted	Fed
Insulin				
PPN	5.8 ± 1.2	10.9 ± 4.5*	6.1 ± 1.2	13.7 ± 4.4*
PPN + rGH	7.6 ± 1.8	13.2 ± 5.6*	6.5 ± 2.7	18.8 ± 11.9*
Growth hormone				
PPN	7.7 ± 5.2	3.1 ± 3.5	2.5 ± 1.5	1.7 ± 1.2
PPN + rGH	9.4 ± 12.8	43.0 ± 17.5*	13.9 ± 2.8	30.5 ± 5.6†
IGF-I				
PPN	96 ± 28	88 ± 31	63 ± 20	90 ± 25
PPN + rGH	111 ± 16	115 ± 10	133 ± 13	134 ± 36

*$P < .05$, †$P < .01$: *v* fasted.

7 days after surgery, using ^{15}N enrichment of urinary urea nitrogen, and showed a postoperative increase in protein breakdown, although the change in protein synthesis was greater in the group receiving rGH supplementation. The greater effect of rGH on nitrogen excretion and whole-body protein synthesis shown in their study compared with the present investigation might be explained by the fact that their patients had perioperative extradural blockade, which has been shown to attenuate postoperative protein breakdown,[28] and received more nitrogen in the PPN solution. The amount of dietary nitrogen used in this study represents a mean maintenance level of intake recommended by the Food and Agricultural Organization (World Health Organization, 1973), and is considered satisfactory for an accepted level of nitrogen retention in the stressed patient.[29] Although the adaptation period to the nutritional regimen studied was to some extent shorter than the recommended 14 days,[30] it was believed that within the ethical constraints of studying patients, a 5- to 7-day period was acceptable.

The ability of growth hormone to conserve nitrogen even when the subjects were fed a normocaloric diet has been previously shown by Ziegler et al,[9] who administered rGH to a mixed group of trauma patients and observed a decrease in nitrogen excretion. Similarly, Douglas et al,[8] assessing the effect of rGH on postoperative whole-body protein metabolism in the postabsorptive state, showed a conservation of nitrogen and suggested that the decrease in nitrogen excretion seen when rGH was given with parenteral nutrition was due to increased synthesis and not to decreased catabolism. With the present investigation conducted in the fasted and fed states, we were able to observe significant attenuation in amino acid oxidation in the group receiving rGH supplementation. This would result in amino acids being made available for incorporation into new proteins. To some extent, this could explain the role of rGH in the modulation of protein synthesis and the net effect on protein breakdown.

A quantitative discrepancy between the rate of postoperative leucine oxidation and urinary nitrogen excretion was observed in the present study. We do not have a direct explanation for this; however, others have found a poor correlation between urea excretion and amino acid oxidation as measured by $^{13}CO_2$ in a group of volunteers receiving IV feeding.[31] A strict comparison between urinary nitrogen excretion and labeled leucine oxidation cannot be made, since several variables have to be taken into account, such as interrupted feeding, urinary collection over a 24-hour period, and leucine kinetics performed over a limited period (8 hours) reflecting both the postabsorptive and fed state.

Another important finding of this study was that an IV mixture of protein, lipid, and carbohydrate was associated with an overall significant increase in leucine oxidation and a reduction in net protein breakdown. No changes in whole-body protein synthesis were observed as a result of feeding. Measurement of whole-body protein metabolism assessed by the disappearance of labeled leucine from the plasma has given rise to differing conclusions. Previous studies in volunteers[19,20] have suggested that the rate of protein synthesis was increased in the fed state compared with the fasting state. However, a range of other studies using essentially the same methodology have reported no stimulation of whole-body protein synthesis with feeding, but instead a large decrease in net body protein breakdown.[18,21] The above studies were conducted in healthy volunteers given hourly oral nutrients, whereas the present investigation was undertaken in stressed subjects using IV nutrition—implying that a direct comparison cannot be made. It is interesting that the response to IV feeding before or after surgery was consistent in all patients studied, indicating that utilization of nutrients in the stressed patient is directed mainly toward sparing the net protein breakdown instead of modulating the synthesis. Although the nitrogen intake used in this study was well below that used in the volunteer studies, the present findings support the beneficial role of nutrition in the stressed patient and highlights the necessity of assessing protein metabolism during fasted and fed states with regard to the quality of nutrients used during the postoperative period.

The significant decrease in the RQ observed after surgery in the PPN + GH group is in agreement with a previous observation[32] indicating the effect of rGH on lipid oxidation and the utilization of fatty acids as an energy source to favor protein synthesis.

Although the present data provide strong evidence that rGH effects are mediated primarily by modulating whole-body amino acid oxidation and protein synthesis in both fasted and fed states, the mechanisms by which rGH increases protein synthesis in the surgical patient are yet to be established. Feeding with or without rGH was accompanied by a significant increase in plasma insulin. The significant postoperative increase in circulating insulin concentration in rGH-treated patients is consistent with the notion that rGH and stress cause insulin resistance with respect to carbohydrate metabolism. Resistance to glucose does not necessarily imply a resistance to the effect of insulin on protein kinetics.[33] It is possible that the increased plasma insulin was responsible for the decrease in protein breakdown observed with feeding.

Rather than acting via a mechanism that increases insulin, growth hormone may be responsible for its anabolic action, through a direct stimulation of IGF-I.[11] In the present study, the plasma concentration of IGF-I decreased in the postoperative period despite a moderate intake of protein. This finding confirms the negative effect of surgical stress on IGF-I production, which can be attenuated by a high energy and protein intake.[34,35]

In this group of surgical patients receiving rGH, circulating concentrations of IGF-I were increased after surgery, suggesting a more likely role of IGF-I in the observed anabolic effect on rGH therapy. Recent studies have confirmed the anabolic effects of recombinant human IGF-I in animals and humans under different conditions of catabolism.[36,37]

The present study provides a rationale for the evaluation of rGH therapy during fasted and fed states in surgical patients in need of nutritional support. It will be necessary to explore the effective dose of rGH to reverse the protein catabolic effects, and to determine whether the anabolic effects are preserved over time.

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