Intravenous Glutamine Does Not Stimulate Mixed Muscle Protein Synthesis in Healthy Young Men and Women

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We investigated the effects of a glutamine-supplemented amino acid mixture on vastus lateralis muscle protein synthesis rate in healthy young men and women. Three men and 3 women (27.8 ± 2.0 yr, 22.2 ± 1.0 body mass index [BMI], 56.1 ± 4.5 kg lean body mass [LBM]) received a 14-hour primed, constant intravenous infusion of L[1-^{13}C]leucine to evaluate the fractional rate of mixed muscle protein synthesis. In addition to tracer administration, a clinically relevant amino acid mixture supplemented with either glutamine or glycine in amounts isonitrogenous to glutamine, was infused. Amino acid mixtures were infused on separate occasions in random order at a rate of 0.04 g/kg/h (glutamine at ~0.01 g/kg/h) with at least 2 weeks between treatment. For 2 days before and on the day of an infusion, dietary intake was controlled so that each subject received 1.5 g protein/kg/d. Compared with our previous report in the postabsorptive state, amino acid infusion increased the fractional rate of mixed muscle protein synthesis by 48% ($P < .05$); however, the addition of glutamine to the amino acid mixture did not further elevate muscle protein synthesis rate (ie, 0.071% ± 0.008%/h for amino acids + glutamine *v* 0.060% ± 0.008%/h for amino acids + glycine; $P = .316$). Plasma glutamine concentrations were higher ($P < .05$) during the glutamine-supplemented infusion, but free intramuscular glutamine levels were not increased ($P = .363$). Both plasma and free intramuscular glycine levels were increased when extra glycine was included in the infused amino acid mixture (both $P < .0001$). We conclude that intravenous infusion of amino acids increases the fractional rate of mixed muscle protein synthesis, but addition of glutamine to the amino acid mixture does not further stimulate muscle protein synthesis rate in healthy young men and women.

MUCH OF THE understanding of the dynamics of human skeletal muscle protein turnover has been derived from measures of the synthesis rate of mixed muscle protein using stable isotope tracer techniques.[1] Using this approach we have shown that age,[2] exercise and hormonal status,[2-5] and disease[6] all significantly impact mixed muscle protein synthesis rate in humans. Currently, we are interested in nutritional control of human muscle protein synthesis.

Infusion of a mixed amino acid solution in the postabsorptive state stimulates mixed muscle protein synthesis.[7-9] This stimulatory effect of amino acids is due mainly to essential amino acid components.[10,11] There is little evidence to suggest that nonessential amino acids stimulate muscle protein synthesis.[11] However, glutamine, which is a nonessential amino acid, may represent a special case. It is the most abundant free amino acid in skeletal muscle, and it maintains special metabolic features that may be important for muscle protein balance (reviewed in Hall et al[12]). In laboratory animals, a positive association between muscle-free glutamine levels and muscle protein synthesis rate has been established.[13] MacLennan et al[14] reported that increasing the glutamine concentration in rat hindlimb perfusate increased the rate of hindlimb muscle protein synthesis. In humans, muscle-free glutamine levels decrease after elective surgical trauma,[15] and this correlates to a decrease in the polyribomose concentration in muscle (a surrogate for protein synthetic potential). While glutamine nutrition can attenuate the postoperative decline in muscle-free glutamine and protein synthesis,[16] at present it is unclear whether relationships between glutamine nutrition, muscle-free glutamine, and protein synthesis are coincidental or mechanistic.

A first step in understanding the potential for glutamine to stimulate skeletal muscle protein synthesis is to evaluate its effect in normal, healthy humans. Therefore, the purpose of this study was to determine if glutamine, when added to a standard mixture of amino acids, would accelerate mixed muscle protein synthesis rate in healthy young adults.

SUBJECTS AND METHODS

Subjects

Six healthy adults (3 men and 3 women) volunteered to participate in this study. Their mean age was 27.8 ± 2.0 (SE) years, height was 172.1 ± 3.8 cm, weight was 65.8 ± 3.7 kg, and body mass index (BMI) was 22.2 ± 1.0 kg/m^2. Body composition was determined by underwater weighing.[17] Percent body fat and lean body mass (LBM) averaged 15.3% ± 3.1% and 56.1 ± 4.5 kg, respectively. Study design, purpose, and possible risks were explained to each subject before written informed consent was obtained. The Institutional Review Board and General Clinical Research Center review committees of the Washington University School of Medicine approved this study.

Experimental Protocol

This study was designed to determine whether glutamine, when provided with a background mixture of amino acids, accelerates the fractional rate of mixed skeletal muscle protein synthesis. Each subject was studied twice, once during an overnight (14-hour) infusion of a mixed amino acid solution that contained glutamine, and during a second infusion when the amino acid mixture was supplemented with glycine in an amount isonitrogenous to glutamine. The order was randomized, and study days were separated by ≥2 weeks.

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Submitted December 14, 1999; accepted May 1, 2000.

Supported by National Institutes of Health (NIH) Grants No. AG-00078, AG-00444, RR-00954, RR-00036, DK-20579, DK-54163, and by a grant from the American Federation for Aging Research (AFAR).

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0026-0495/00/4912-0007$10.00/0

doi:10.1053/meta.2000.18524

Amino Acid Solutions

Concentrations in the stock amino acid solution (6.5% RenAmin; Clintec Nutrition, Deerfield, IL) are provided in Table 1. Amino acid mixtures were freshly prepared and infused at a rate of 0.03 g/kg/h. In 1 case, glutamine was added to this mixture to achieve a glutamine infusion rate of 0.01 g/kg/h, and in the second condition, an isonitrogenous amount of glycine was added in place of glutamine. Thus, the total amino acid infusion rate for both trials was approximately 0.04 g/kg/h and provided approximately 42 g of amino acids over a 14-hour period. This total amount of amino acid delivery has previously been shown to increase the rate of mixed skeletal muscle protein synthesis.[8,9] The calculated osmolarity of each amino acid mixture was between 300 to 400 mOsm/L.

Dietary Control

A research dietician interviewed each subject and assessed their typical food and caloric consumption patterns and designed a 3-day weight maintenance meal plan that consisted of 1.5 g protein/kg/d and 147 to 168 kJ (35 to 40 kcal)/kg/d. These meals (3 daily and snacks) were prepared and served to each subject in the General Clinical Research Center. The subjects were instructed to eat no other food and to eat all food provided. Any small amount not consumed was weighed, and the daily intake record was corrected. Controlled feeding began 2 days before each of the infusion experiments.

Isotope Infusion for Whole Body Protein Turnover and Mixed Skeletal Muscle Protein Synthesis Rate

On the evening of the third day of the controlled meal plan, subjects were admitted to the Inpatient Unit of the General Clinical Research Center. Catheters were inserted into a forearm vein of each arm for blood sampling and infusion of isotope and amino acids. After obtaining baseline blood and breath samples, a primed (7.59 μmol/kg body weight) constant intravenous infusion (7.59 μmol/kg/h) of L[1-^{13}C]leucine (~99 atom%; MassTrace, Woburn, MA) was started and used to estimate whole body protein breakdown, synthesis, and amino acid oxidation rates using the reciprocal pool approach[18] and to determine the in vivo rate of incorporation of [^{13}C]leucine into mixed skeletal muscle protein.[19,20] The mixed amino acid infusion containing either glutamine or extra glycine was started in conjunction with L[1-^{13}C]leucine infusion, which was begun at the time of the evening meal (6:00 PM) and continued throughout the night until 8:00 AM the next morning. After finishing their evening meal, subjects were allowed to consume only water until the end of the infusion experiment. Thus, the subjects transitioned from a postprandial to postabsorptive state during the course of isotope and amino acid infusion.

Table 1. Concentration of Amino Acids in RenAmin Stock Solution Used for Amino Acid Infusion

Amino Acid	g/L
Essential amino acids	
Valine	8.2
Leucine	6.0
Isoleucine	5.0
Methionine	5.0
Phenylalanine	4.9
Lysine	4.5
Histidine	4.2
Threonine	3.8
Tryptophan	1.6
Arginine	6.3
Nonessential amino acids	
Alanine	5.6
Proline	3.5
Glycine	3.0
Serine	3.0
Tyrosine	0.4

NOTE. As reported by Clintec Nutrition, Deerfield, IL.

In addition to that obtained at baseline, blood samples were drawn every 30 minutes during the last 3 hours of infusion. A small portion (~0.5 mL) of each blood sample was immediately centrifuged and analyzed for plasma glucose concentration (Beckman Instruments, Fullerton, CA). The remaining blood was placed on ice and centrifuged later. Plasma was stored at −20°C for subsequent analysis of insulin and amino acid concentrations, and ^{13}C enrichment in leucine and α-ketoisocaproic acid (KIC). Additional blood was taken at baseline and during the last hour of infusion for the measurement of plasma ammonia concentration. A 15-minute determination of CO_2 production rate was made, in the morning at 6:30 AM, using a ventilated hood indirect calorimetry system. Expired breath for $^{13}CO_2/^{12}CO_2$ determination was collected immediately after the indirect calorimetry procedure. With the use of sterile technique and local anesthesia, muscle samples (50 mg) were obtained from the vastus lateralis muscle using a 6-mm Bergstrom biopsy needle (DePuy, Warsaw, IN). The first muscle sample was obtained 90 minutes after the start of infusions and a second sample, from the contralateral vastus lateralis, at the end of infusion. Time between muscle samples was documented (approximately 12 hours).

Sample Analyses

Plasma (0.5 mL) for determination of ^{13}C-leucine enrichment was applied to a cation exchange resin (Dowex AG-50W X8, 100 to 200 mesh H^+ form). After washing with 0.01 mol/L hydrochloric acid (HCL), amino acids were eluted with 6 mol/L NH_4OH, and the *N*-acetyl *n*-propyl ester was prepared as previously described.[21] Plasma KIC was isolated and chemically derivatized as previously described.[22] Gas chromatography-positive chemical ionization quadrupole mass spectrometry was used to determine [1-^{13}C] abundance in leucine (m/z 216 and 217), while electron impact ionization was used for [^{13}C]KIC (m/z 232 and 233) determination. Insulin was determined in duplicate using a double-antibody radioimmunoassay method.[23] Plasma ammonia concentration was determined using the bromophenol blue colormetric method (Johnson & Johnson Clinical Diagnostics, Rochester, NY).

Plasma amino acid concentrations were determined by high-performance liquid chromatography (HPLC) using a Waters (Milford, MA) controller/pump system (model 600E) equipped with a scanning fluorescence detector (model 474). Data were acquired and processed with Millennium v2.10 software (Waters). Samples were prepared by centrifuging 0.5 mL of plasma in Centrifree micropartition tubes (Amicon, Beverly, MA) at 1,000×*g*, 4°C for 30 minutes. OPA (o-phthalaldehyde) derivatives were prepared by combing 5 μL of filtered plasma with 20 μL fluoraldehyde (Pierce, Rockford, MA) and 5 μL 300 mmol/L norleucine (internal standard). Mixtures were vortexed and incubated for 3 minutes at room temperature. Lastly, 10 μL 100 mmol/L sodium acetate buffer was added. Derivatized samples (15 μL) were manually injected on a Chrompack (Middleburg, The Netherlands) 3-μm Microsphere C_{18} column (10 cm × 4.6 mm [inner diameter (id)], protected by a reverse phase guard column (1 cm × 2.0 mm [id]) from the same supplier.

Exhaled breath samples were collected into 20-mL evacuated tubes (Terumo Medical, Elkton, MD). These samples were analyzed for $^{13}CO_2/^{12}CO_2$ enrichment (*m/z* 45 and 44 ions) using a dual-inlet isotope ratio mass spectrometer (SIRA Series II, VG Isogas, Windsford, UK).

Muscle samples (15 to 30 mg) were powdered under liquid nitrogen and then homogenized in 1 mL 10% trichloroacetic acid (TCA). The homogenate was centrifuged and the supernatant used for the determination of intramuscular-free amino acid concentrations. Intramuscular-free amino acid concentrations in the TCA supernatant were determined

by HPLC as described above. The protein pellet was washed 4 times with 1 mL normal saline. After removal of saline, 1 mL of 6 mol/L HCL was added and the pellet was hydrolyzed at 110°C for 18 to 24 hours. Muscle [^{13}C]leucine enrichment was measured in the hydrolyzed mixed muscle protein as the *N*-acetyl *n*-propyl ester using capillary gas chromotography-combustion isotope ratio mass spectrometry.[20]

Calculations and Statistics

Plasma [^{13}C]KIC enrichment was used to calculate the rate of whole body leucine turnover.[24] This value was also used as the precursor pool enrichment for the calculation of the fractional rate of mixed muscle protein synthesis.[25] Whole body protein breakdown was estimated by subtracting the infusion rate of exogenous unlabeled leucine from the whole body leucine turnover rate. The ^{13}C enrichment in CO_2 in conjunction with the CO_2 production rate determined by indirect calorimetry was used to estimate the whole body leucine (protein) oxidation rate.[26] The difference between the whole body protein breakdown rate and the leucine oxidation rate is the nonoxidative disposal rate of leucine and is representative of whole body protein synthesis rate.[26]

All results are presented as mean ± SE. Paired *t* tests were used to compare values from the glutamine and glycine infusion trials. Analysis of variance was used to compare the change in plasma ammonia levels from pre- to postinfusion. Unpaired *t* tests were used to compare plasma amino acid concentrations and muscle protein synthesis rates from previously studied subjects who had fasted[2] with those obtained during amino acid infusion in the present study. Experimental conditions, such as timing of the evening meal and length of isotope infusion for this comparison study, were identical to those described herein. Plasma samples from these separate studies were batched and analyzed together by HPLC for amino acid concentration. Differences were considered significant at $P < .05$.

RESULTS

Concentrations of selected essential amino acids did not differ during the glutamine and glycine amino acid infusion studies (Table 2). The sum of all essential amino acid concentrations also did not differ between the 2 amino acid infusion trials. Amino acid infusion with added glutamine ($P < .01$) or glycine ($P < .0001$) resulted in higher plasma levels of these nonessential amino acids, respectively (Table 3). Plasma serine concentration was lower during the glutamine trial ($P < .01$), while plasma levels of alanine and tyrosine were similar during the 2 amino acid infusion trials. The sum of all measured nonessential amino acid concentrations was higher ($P < .01$) during the glycine trial due to the substantial increase in plasma glycine.

Table 2. Plasma EAA Concentrations During Amino Acid Infusion With Added Glutamine or Glycine

	Glutamine Trial	Glycine Trial	Control
Valine	425.1 ± 12.8*	408.7 ± 19.2*	257.8 ± 13.7
Leucine	183.3 ± 7.9	182.5 ± 9.9	185.7 ± 8.6
Isoleucine	98.4 ± 4.2*	97.0 ± 5.0*	68.9 ± 3.0
Methionine	72.3 ± 1.9*	69.9 ± 3.9*	29.5 ± 2.2
Phenylalanine	73.9 ± 2.3*	72.8 ± 4.2*	58.3 ± 3.9
Histidine	128.5 ± 3.4	125.1 ± 8.1	121.6 ± 5.0
Threonine	201.2 ± 16.4	196.5 ± 22.2	187.0 ± 10.8
Arginine	110.9 ± 5.1	105.2 ± 9.1	122.5 ± 9.9
Sum EAA	1,294 ± 21.7*	1,257.7 ± 69.2*	1,034.5 ± 30.0

NOTE. Control values from previously studied subjects[2] who had a determination of mixed muscle protein synthesis in the postabsorptive state are also provided. See Subjects and Methods for details. n = 6 for each condition and values are means ± SE expressed in μmol/L.

Abbreviation: EAA, essential amino acid.

*Significantly different ($P < .05$) from control.

Table 3. Plasma NEAA Concentrations During Amino Acid Infusion With Added Glutamine or Glycine

	Glutamine Trial	Glycine Trial	Control
Alanine	388.3 ± 22.0	365.9 ± 33.7	409.2 ± 22.6
Serine	120.1 ± 5.7*†	167.6 ± 9.9	159.9 ± 11.6
Tyrosine	45.3 ± 3.0*	45.2 ± 3.8*	65.8 ± 3.1
Glutamine	637.1 ± 12.3†	565.2 ± 22.7	544.8 ± 68.5
Glycine	250.0 ± 29.2†	600.6 ± 29.4*	360.3 ± 73.2
Sum NEAA	1,440.8 ± 63.7†	1,739.5 ± 76.7*	1,540.0 ± 141.8

NOTE. Control values from previously studied subjects[2] who had a determination of mixed muscle protein synthesis in the postabsorptive state are also provided. See Subjects and Methods for details. n = 6 for each condition and values are means ± SE expressed in μmol/L.

Abbreviation: NEAA, nonessential amino acid.

Significantly different ($P < .05$) from: *control, †glycine.

For comparison purposes, we also measured plasma amino acid concentrations in stored plasma samples from a separate group of subjects who had previously undergone postabsorptive mixed muscle protein synthesis measurements.[2] Compared with these controls, amino acid infusion increased plasma concentrations of valine ($P < .0001$), methionine ($P < .0001$), isoleucine ($P < .001$), and phenylalanine ($P < .01$). This pattern of elevation in essential amino acids was generally in proportion to the concentration of individual amino acids in the infusate (see Table 1). Additionally, the sum of all plasma essential amino acids was higher in the amino acid-infused conditions. The addition of glycine, but not glutamine, to the standard amino acid mixture resulted in significantly higher plasma levels in comparison to controls. Except for higher levels of tyrosine in the postabsorptive condition, the concentration of the other measured nonessential amino acids was similar to those observed during the amino acid infusion trials (Table 3).

Addition of glycine or glutamine to the amino acid mixture did not alter plasma glucose concentration (data not shown). Likewise, plasma insulin was not effected by the type of amino acid infusion and remained within normal fasting limits during both trials (ie, 5.0 ± 0.8 μU/mL during glutamine and 4.6 ± 0.2 μU/mL during the glycine trial). Plasma ammonia levels did not increase significantly during the amino acid infusion trials and concentrations were not different at the end of the glutamine and glycine conditions averaging 33.1 ± 2.5 and 30.8 ± 3.1 μmol/L, respectively.

Compared with our previous measurements in the postabsorptive state,[2] amino acid infusion significantly increased the rate of vastus lateralis mixed muscle protein synthesis (Fig 1). However, addition of glutamine to the amino acid mixture did not further increase muscle protein synthesis rate. The fractional rate of mixed muscle protein synthesis determined during the glutamine trial was 0.071% ± 0.008%/h, while during the glycine-supplemented condition, it was 0.060% ± 0.008%/h ($P = .316$). Isotopic enrichment data used for the calculation of mixed muscle protein synthesis are presented in Table 4. Free intramuscular glutamine levels were elevated slightly during the glutamine-supplemented condition, averaging 7.91 ± 0.68 μmol/g wet weight (ww) muscle versus 7.39 ± 0.47 μmol/g ww

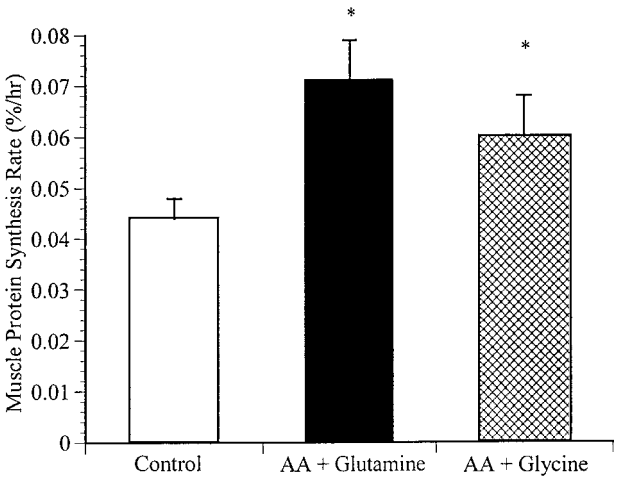

Fig 1. The fractional rate of vastus lateralis mixed muscle protein synthesis in healthy young men and women in the postabsorbtive state (control) and during amino acid (AA) infusion with added glutamine or glycine. Data for control subjects were obtained from a previously published study.[2] n = 6 for each condition; *$P < .05$, significantly greater than control.

muscle during the glycine trial, but this was not significantly different ($P = .363$). On the other hand, free intramuscular glycine levels were significantly elevated during the glycine-supplemented amino acid infusion, averaging 0.96 ± 0.09 μmol/g ww muscle versus 0.47 ± 0.07 μmol/g ww muscle for the glutamine trial ($P < .001$).

Whole body protein turnover rates did not differ during the glutamine- and glycine-supplemented amino acid infusion trials averaging 151 ± 6 μmol/kg LBM/h and 153 ± 2 μmol/kg LBM/h, respectively. Likewise, leucine oxidation rates were not different, averaging 37 ± 3 μmol/kg LBM/h for the glutamine trial and 39 ± 3 μmol/kg LBM/h during the glycine trial. Accordingly, calculated rates of whole body protein breakdown and synthesis were remarkably similar during the glutamine- and glycine-supplemented amino acid infusion trials (data not shown).

DISCUSSION

We examined the response of human skeletal muscle protein synthesis to intravenously infused amino acids. We hypothesized that glutamine, when added to a standard mixture of amino acids, would stimulate the rate of muscle protein synthesis more than an isonitrogenous amino acid mixture without glutamine. As had been previously reported,[7-9] we found that an intravenous infusion of amino acids increased the rate of mixed muscle protein synthesis above that observed in a postabsorptive state. However, when glutamine was added to the intravenous amino acid mixture, the rate of vastus lateralis mixed muscle protein synthesis was not increased further.

In laboratory rodents, glutamine infusion increased free intramuscular glutamine levels and muscle protein synthesis rate.[14] Also in rodents, depletion of the intramuscular glutamine pool was associated with reduced rates of muscle protein synthesis.[13] This is similar to the clinical observation that intramuscular glutamine levels are low after surgery or trauma,[27,28] and that glutamine-supplemented total parental nutrition counteracted the postoperative decline in capacity for muscle protein synthesis,[16] as judged by ribosomal analysis. However, the current investigation strongly suggests that when glutamine-supplemented amino acids are intravenously administered to young healthy men and women, the rate of mixed muscle protein synthesis was not increased to any greater extent than when an isonitrogenous amino acid mixture (not containing glutamine) was administered. This indicates that when muscle protein synthesis rate is stimulated with an intravenous mixture of essential and nonessential amino acids, addition of glutamine will not accentuate this response. Alternatively, the findings could be interpreted to suggest that omission of glutamine from an intravenous amino acid infusion will not limit the stimulatory effect of hyperaminoacidemia on mixed muscle protein synthesis rate. It is important to note that these conclusions are based on our observation in a healthy population of young men and women and may not be applicable to critical conditions when free muscle glutamine is reduced, such as in the studies of Hammarqvist et al[16] and Wernerman et al.[15]

There are a couple of caveats worth noting. The mean values for both muscle protein synthesis and free intramuscular glutamine levels were slightly, but not significantly, higher during the glutamine infusion trial. It is possible that if we had run more studies, these differences may have become statistically significant. Even so, a more likely explanation is that a major fraction of the infused glutamine was either partially or completely oxidized.[29] Our findings indirectly support this because when glycine, another nonessential amino acid, was added to the amino acid mixture in amounts isonitrogenous to glutamine, we observed significant elevations in both plasma and free intramuscular glycine levels. This suggests the infused

Table 4. Individual ^{13}C Enrichment Values for Plasma KIC and Mixed Muscle Protein

		^{13}C-KIC, Atom % Excess		^{13}C-Leucine Increment, Atom % Excess	
Subject No.	Sex	Glutamine Trial	Glycine Trial	Glutamine Trial	Glycine Trial
1	Female	5.39	5.41	.0583	.0385
2	Male	6.13	5.81	.0495	.0506
3	Female	5.65	5.48	.0440	.0484
4	Male	5.40	5.35	.0242	.0242
5	Male	5.21	5.24	.0583	.0253
6	Female	6.80	6.18	.0693	.0605
Mean ± SE		5.76 ± 0.24	5.58 ± 0.14	.0506 ± .006	.0413 ± .006

NOTE. ^{13}C enrichment for plasma KIC are means of 7 values taken at isotopic plateau during the final 3 hours of infusion.

glutamine was metabolically more labile, and that it may not be possible to elicit elevations in free intramuscular glutamine in healthy young men and women. While dose response studies addressing the safety and efficacy of glutamine infusion to increase plasma glutamine levels have been conducted,[30] we are unaware of any dose response studies specifically addressing the free intramuscular glutamine pool. Our glutamine infusion rate was equivalent to that shown to be effective in preventing a postoperative decline in muscle-free glutamine levels.[16,31] Still, it is conceivable we achieved maximal nutritional stimulation of muscle protein synthesis in our young healthy subjects by providing adequate quantities of essential amino acids, masking any potential benefit of glutamine supplementation to increase the mixed muscle protein synthesis rate. Thus, in the future, it will be important to conduct studies, which compare intravenously administered glutamine to specific essential amino acids such as phenylalanine[11] or valine[10] to isolate its ability to stimulate mixed muscle protein synthesis in healthy men and women.

The exact mechanism(s) by which amino acids stimulate muscle protein synthesis rate are unknown, but likely involve increased delivery and subsequent transport of amino acids across the muscle cell membrane to supply the necessary complement of amino acids and energy for protein synthetic processes. It appears that essential amino acids are particularly important for the stimulation of human muscle protein synthesis. Smith et al[11] reported that flooding doses of essential (phenylalanine, threonine) amino acids increased the rate of vastus lateralis mixed muscle protein synthesis in healthy humans, but that flooding doses of nonessential (glycine, serine) amino acids did not. Similarly, Tipton et al[32] reported that muscle protein synthesis rates after resistance exercise were equally stimulated when subjects consumed an essential amino acid solution or a mixed amino acid solution, which included both essential and nonessential amino acids. Our data extend these observations and suggest that glutamine, 1 of the most metabolically active nonessential amino acids, was not required for the stimulation of mixed muscle protein synthesis rate in healthy young men and women.

In the present investigation, we did not determine the rate of muscle protein breakdown. An earlier report emphasized that intravenously infused amino acids accelerated the rate of muscle protein synthesis, while having no effect on muscle protein breakdown.[9] Thus, the positive protein balance in muscle subsequent to intravenous amino acid nutrition is likely a result of an increased muscle protein synthesis rate. Nonetheless, we have not eliminated the possibility that addition of glutamine to intravenously infused amino acid solutions may reduce the rate of muscle protein breakdown[33] and thereby result in a more positive net balance of muscle protein.

The results of this study should not be taken to mean that intravenous glutamine does not play an important role in the regulation of muscle protein turnover. We have recently reported that plasma glutamine rate of appearance was accelerated in acquired immune deficiency syndrome (AIDS) patients with muscle wasting.[6] Also, it is known that the metabolic stress associated with surgery, trauma, or critical illness results in a loss of lean tissue, secondary to a lowering of the free muscle glutamine pool.[16,27,28] Intracellular concentrations of free amino acids may modulate the rate of skeletal muscle protein breakdown,[34] and in particular, low levels of muscle free glutamine or accelerated rates of glutamine efflux from muscle may be important signals for increased muscle proteolysis. Thus, elevating muscle-free glutamine content from low to normal levels through increased exogenous delivery may have a more profound impact on skeletal muscle protein balance than an elevation of muscle-free glutamine to higher than normal levels. More detailed studies on glutamine inward and outward transport and their effects on human skeletal muscle protein synthesis rate and balance under conditions of metabolic stress are required.[35]

In summary, the findings show that intravenous provision of amino acids stimulates mixed muscle protein synthesis in healthy humans. Addition of glutamine to the intravenous amino acid mixture increased plasma glutamine levels, but not the intramuscular-free glutamine concentration. Mixed muscle protein synthesis rate was not further enhanced with the addition of glutamine.

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