Effect of Amino Acids and Glucose on Exercise-Induced Gut and Skeletal Muscle Proteolysis in Dogs

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The effect of amino acid and/or glucose administration before and during exercise on protein metabolism in visceral tissues and skeletal muscle was examined in mongrel dogs. The dogs were subjected to treadmill running (150 minutes at 10 km/h and 12% incline) and intravenously infused with a solution containing amino acids and glucose (AAG), amino acids (AA), glucose (G) or saline (S) in randomized order. The infusion was started 60 minutes before exercise and continued until the end of the exercise period. An arteriovenous-difference technique was used to estimate both tissue protein degradation and synthesis. When S was infused, the release of leucine (Leu) from the gut and phenylalanine (Phe) from the hindlimb significantly increased during exercise, thus indicating that exercise augmented proteolysis in these tissues. The balance of Leu across the gut during exercise demonstrated a net uptake with both AAG and AA, whereas a net release was observed for G and S. In addition, Leu uptake in the gut during the last 90 minutes of the exercise period tended to be greater with AAG versus AA ($P = .06$). Phe balance across the hindlimb during the late exercise period showed a significant release with S, AA, and G, whereas the balance with AAG did not show a significant release. These results suggest that exercise-induced proteolysis in the gut may be reduced by supplementation with AA, and this effect may be enhanced by concomitant G administration. However, in skeletal muscle, both AA and G may be required to prevent net protein degradation during exercise. G provided without AA did not achieve net protein synthesis in either tissue.
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EXERCISE REPORTEDLY AUGMENTS skeletal muscle protein breakdown.[1-4] The protein content of the liver was shown to be decreased in rats who ran to exhaustion.[5] The release of α-aminonitrogen from the gut is increased as a result of increased gut protein degradation in exercising dogs.[6,7] Some amino acids (AA) such as branched-chain amino acids (BCAA) have been reported to be an important energy source in contracting skeletal muscle during exercise. Visceral tissues play an important role as a source of BCAA for skeletal muscle during exercise.[8] The elevated release of BCAA from the splanchnic bed has also been shown during exercise in humans, which demonstrates that splanchnic tissues are the site of protein catabolism and thereby a source of AA for peripheral tissues.[9,10] These results indicate that exercise induces proteolysis in splanchnic tissues and in skeletal muscle.

Some previous reports have shown that administration of carbohydrates during exercise decreases protein degradation.[11,12] Protein breakdown in skeletal muscle has been shown to be decreased after administration of BCAA.[13] However, little information is available as to whether carbohydrates reduce exercise-induced proteolysis in splanchnic tissues. In addition, the effect of AA supplied with or without carbohydrates on protein degradation induced by exercise remains to be elucidated.

The aim of the present study was therefore to examine whether AA supplied either separately or simultaneously can reduce exercise-induced proteolysis in splanchnic tissues and skeletal muscle.

MATERIALS AND METHODS

Animals and Surgical Procedures

Ten male mongrel dogs were used (age, 11 months, mean weight, 17.0 ± 0.6 kg). The dogs were maintained on a standard diet (450 g/d Oriental CD; Oriental Yeast, Tokyo, Japan: 46.8% carbohydrate, 26.5% protein, 8.7% fat, and 3.6% fiber based on dry weight). All animals were gradually acclimated to running on a treadmill before surgery, and each animal was subjected to exactly the same exercise protocol used for the study before surgery to verify whether they could indeed run for the duration and at the intensity of the exercise regimen used in the experiment.

At least 14 days before the experiment, surgery was performed under general anesthesia (pentobarbital sodium 25 mg/kg) under sterile conditions.[14] Silastic sampling catheters (1.0 mm ID) were inserted into the femoral artery, portal vein, left common hepatic vein, and femoral vein. In addition, a silastic catheter (1.0 mm ID) was inserted into the external jugular vein for infusion of the test solutions. After insertion, the catheters were filled with heparinized saline (100 U/mL). The free ends of the catheters were knotted. Doppler flow probes were used to measure the blood flow of the portal vein, hepatic artery, and external iliac artery.[6,15] The Doppler flow cuff leads and knotted catheter ends were placed in subcutaneous pockets so that complete closure of the skin was possible. Thereafter, animals with a leukocyte count less than 18,000/μL, a hematocrit value above 35%, a good appetite, and normal stools were used.

On the day of the experiment, after overnight fasting, the catheters buried in subcutaneous pockets were freed through a small skin incision made under local anesthesia (2% lidocaine hydrochloride). The contents of each tube were aspirated, and then the catheters were flushed with heparinized saline (6 U/mL).

Test Solutions

Solutions containing both AA and glucose (AAG), AA, glucose (G), or normal saline (S) were tested. The AAG solution was prepared by mixing a 10% G solution (Otsuka Pharmaceutical, Tokyo, Japan) with a 10% AA solution (Amiparen: Otsuka Pharmaceutical; AA concentrations (μmol/mL) in Amiparen: 107 leucine, 61 isoleucine, 68 valine, 72 lysine, 48 threonine, 10 tryptophan, 26 methionine, 42 phenylalanine, 8 cysteine, 3 tyrosine, 60 arginine, 32 histidine, 90 alanine, 43 proline, 29 serine, 79 glycine, 8 aspartic acid, 7 glutamic acid, and 792 total AA) at a 1:1 ratio. The AA solution was made by diluting the 10% AA solution

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(Amiparen) with an equal volume of 0.9% saline. For the G solution, a 10% G solution (Otsuka Pharmaceutical) was used.

Experimental Procedures

The outline of the experiment is shown in Fig 1. The experiment consisted of a 120-minute rest period and 150-minute exercise period. The rest period was subdivided into a basal period (−120 to −60 minutes) when saline was infused into the jugular vein at 10 mL/kg/h and a sedentary period of infusion with either the AAG, AA, G, or S solution at 10 mL/kg/h into the jugular vein. Infusion of the test solution starting at the beginning of the sedentary period was continued throughout the following 150-minute exercise period. The exercise period was also divided into two parts, the early period and the late period. The work rate used (10 km/h at 12% incline) was of moderate intensity and elicited a twofold increase in the heart rate.[6] Blood samples were obtained using heparinized syringes from the femoral artery, femoral vein, portal vein, and hepatic vein during the basal period (−60 minutes), sedentary period (0 minutes), early exercise period (30 and 60 minutes), and late exercise period (105 and 150 minutes). Blood flow in the external iliac artery, portal vein, and hepatic artery was measured continuously with the Pulsed Doppler Flow/Dimension System (VF-1 coupled with Doppler Module, model DM-1; Crystal Biotech, Holliston, MA) and a MacLab/4 data recording system (ADInstruments, Castle Hill, New South Wales, Australia) using the Cart version 3.3 software package (ADInstruments) to calculate the blood flow. The experiments were performed using a crossover design in randomized order. Each study was separated by greater than 2 weeks. For four dogs in the G and S treatments, blood samples from one or more catheters in the vessels were not available. Therefore, values obtained from the other six dogs were used for data analyses for G and S treatments.

Analyses

The collected blood samples were immediately centrifuged at 3,000 rpm for 15 minutes at 4°C to separate the plasma. Plasma samples were stored at −80°C until analyses were performed. The plasma samples (200 μL) for determination of Leu and Phe were deproteinized with 200 μL 3% sulfosalicylic acid containing 400 μmol/L *S*-(2-aminoethyl)-L-cysteine as an internal standard. The supernatant was assayed with an automatic amino acid analyzer (L-8500; Hitachi). Glucose concentrations in plasma samples were analyzed using the enzymatic method (Merck Auto Glucose; Kanto Chemical, Tokyo, Japan). Plasma immunoreactive insulin (IRI) levels were measured using a radioimmunoassay kit (REABEAD; Dinabot, Tokyo, Japan).

Calculations

The net balance of AA across the tissues was calculated as the product of the arteriovenous difference of the AA concentration and tissue blood flow.[6,15] The net hindlimb balance was determined by the formula $(A - F) \cdot A_f$, where A is the arterial concentration, F is the femoral vein concentration, and A_f is the plasma flow of the external iliac artery. The net gut balance was calculated by the formula $(A - P) \cdot P_f$, where P is the portal vein concentration and P_f is the plasma flow of the portal vein. Net hepatic balance was calculated by the formula $(H_f \cdot A + P_f \cdot P) - (H_f + P_f) \cdot H$, where H is the hepatic vein concentration and H_f is the hepatic artery plasma flow. Splanchnic balance was calculated by the formula $(A - H) \cdot (H_f + P_f)$. In addition, the plasma flow of each vessel was calculated as the blood flow · (1 − hematocrit).

The cumulative balance of AA across the tissues during the exercise period was calculated using the trapezoidal method by multiplying the values for tissue balance by the time.

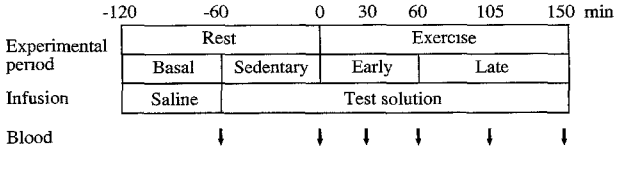

Fig 1. Experimental procedures. The experiment consisted of a 120-minute rest period and a 150-minute exercise period. The rest period was subdivided into a basal period (−120 to −60 minutes) when S was infused into the jugular vein and a sedentary period of infusion with AAG, AA, G, or S into the jugular vein. Infusion of the test solution continued until the end of exercise. The exercise period was divided into an early and a late period. The work rate was 10 km/h at 12% incline. Blood samples were obtained at the time points indicated by arrows.

Statistical Analyses

Statistical assessment of the rest and exercise periods was initially performed using two-way ANOVA for repeated measures. When the ANOVA yielded significant F values ($P < .05$), Fisher's paired least-significant difference test was used for comparisons across all treatments and also for comparing basal and sedentary values with early exercise and late exercise values. Significance was accepted at a P level less than .05. Values are expressed as the mean ± SE.

RESULTS

Blood Flow in Each Vessel

Blood flow in the external iliac artery significantly increased approximately 2.5-fold during exercise in all treatments. However, hepatic artery and portal vein blood flow did not change during the whole experiment. No difference was observed between the treatments.

Plasma Leu, Phe, Glucose, and IRI Concentrations

Arterial Leu concentrations increased after infusion of both the AAG and AA solutions ($P < .05$), and these increases were maintained during the exercise period. However, the concentration of Leu in the G treatment decreased after the start of infusion of the G solution ($P < .05$), and this decrease was thereafter sustained during the exercise period. The concentration of Leu in the S treatment showed a temporal increase during the sedentary period ($P < .05$); however, it decreased to the basal value during exercise (Table 1).

Phe levels also increased significantly after initiating the infusion in AAG and AA treatments ($P < .05$). The concentration of Phe in the G treatment decreased during the sedentary period ($P < .05$), while it gradually increased during exercise and reached a significantly higher level in the late exercise period versus the basal period ($P < .05$). The Phe concentration in the S treatment increased significantly during exercise ($P < .05$) (Table 1).

Plasma glucose levels in both the AAG and G treatments increased after initiating the infusion. These elevated levels decreased during the following exercise period. The glucose concentration in the AA treatment did not change until the early part of exercise; however, it was slightly but significantly lower during the late exercise period versus the basal period ($P < .05$). No significant changes were observed in the S treatment throughout the entire experiment (Table 1).

Plasma IRI levels were elevated after initiating the infusion in AAG, AA, and G treatments ($P < .05$). Although the glucose infusion rate in the G treatment was twice the rate in the AAG

Table 1. Changes in Arterial Plasma Leu, Phe, Glucose, and IRI Concentrations

Parameter		Rest: Basal (−60 min)	Rest: Sedentary (0 min)	Exercise: Early	Exercise: Late
Leu (nmol/mL)	AAG	128 ± 7	485 ± 25^{a*}	422 ± 17^{a*†}	446 ± 12^{a*}
	AA	131 ± 8	585 ± 25^{b*}	488 ± 22^{b*†}	522 ± 21^{b*†}
	G	135 ± 10	71 ± 7^{c*}	87 ± 7^{c*}	81 ± 6^{c*}
	S	138 ± 8	170 ± 10^{d*}	131 ± 8^{c†}	134 ± 6^{d†}
Phe (nmol/mL)	AAG	60 ± 2	219 ± 8^{a*}	261 ± 12^{a*†}	269 ± 10^{a*†}
	AA	60 ± 2	218 ± 7^{a*}	256 ± 8^{a*†}	260 ± 9^{a*†}
	G	59 ± 2	43 ± 3^{b*}	61 ± 4^{b†}	68 ± 2^{b*†}
	S	55 ± 2	62 ± 2^{b}	70 ± 3^{b*†}	71 ± 3^{b*†}
Glucose (mg/dL)	AAG	110 ± 2	141 ± 6^{a*}	112 ± 2^{a†}	121 ± 2^{a*†}
	AA	110 ± 2	107 ± 1^{b}	107 ± 1^{ab}	104 ± 2^{b*}
	G	111 ± 2	182 ± 11^{c*}	121 ± 5^{c†}	131 ± 3^{c*†}
	S	106 ± 2	103 ± 2^{b}	103 ± 1^{b}	100 ± 3^{b}
IRI (μU/mL)	AAG	5.5 ± 1.7	43.1 ± 5.4^{a*}	11.6 ± 2.8^{a†}	12.4 ± 3.4^{a†}
	AA	4.4 ± 0.9	10 6 ± 2.4^{b*}	8.1 ± 2.5^{ab}	5.9 ± 1.5^{b}
	G	3.6 ± 0.8	25.7 ± 4.7^{c*}	5.8 ± 1.1^{ab†}	5.0 ± 1.3^{ab†}
	S	2.4 ± 0.6	3.0 ± 0.7^{b}	1.6 ± 0.4^{b}	2.2 ± 0.4^{b}

NOTE. Data are the mean ± SE; n = 10 dogs for AAG and AA and n = 6 dogs for G and S. Values with different letters are significantly different at $P < .05$ between treatments in the corresponding period.

*$P < .05$ *v* basal.

†$P < .05$ *v* sedentary.

treatment, the mean plasma IRI level during the infusion period was significantly higher in AAG treatment versus G treatment (18.2 ± 3.4 *v* 9.5 ± 1.7 μU/mL, $P < .05$). S treatment showed no significant changes in plasma IRI levels throughout the entire experiment, and the levels were lower compared with the other treatments (Table 1).

Hindlimb Leu Balance

Figure 2A shows the balance of Leu across the hindlimb. No significant uptake or release of Leu across the hindlimb was noted in the basal period for any treatment. Leu balance became positive (net uptake) in the AAG and AA treatments after starting the infusion, and net uptake continued throughout the exercise period. The rate of uptake did not differ between the AAG and AA treatments. On the other hand, the balance in the G and S treatments was not significantly different from zero except for the late exercise period in the S treatment, which showed net uptake. The rate of uptake was significantly higher in the AAG and AA treatments versus G and S treatments during the period when the test solution was infused ($P < .05$).

The cumulative balance of Leu during the exercise period was significantly greater in the AAG and AA treatments versus G and S treatments ($P < .05$). The uptake observed in the AAG and AA treatments was significant ($P < .05$); however, the balance in the G and S treatments was not significant (Table 2).

Gut Leu Balance

Figure 2B depicts the gut balance of Leu. The balance did not differ from zero in the basal period for all treatments. However, a significant net uptake was observed in both the AAG and AA treatments during infusion of each solution ($P < .05$), and the uptake of Leu continued during the exercise period in these two treatments. In addition, the uptake tended to be greater with AAG versus AA during the late portion of the exercise period ($P = .06$). No significant uptake or release occurred in the G and S treatments during the sedentary period. However, the balance turned negative (net release) during the exercise period in these treatments, without any difference between treatments.

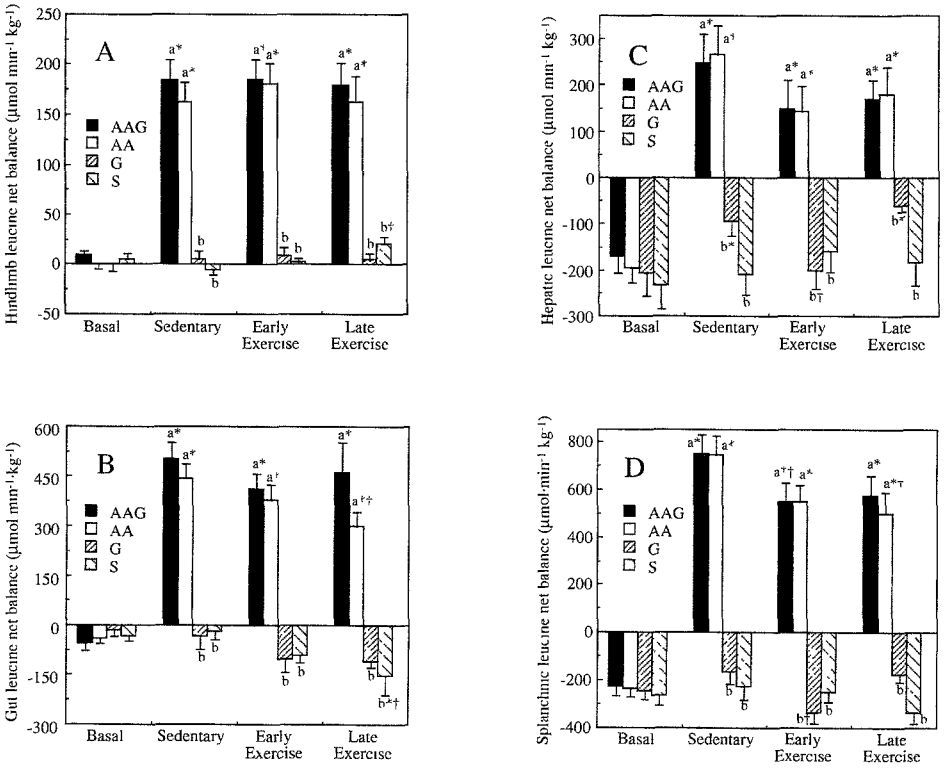

Fig 2. Leu balance across the (A) hindlimb, (B) gut, (C) liver, and (D) splanchnic tissue. Data are the mean ± SE; n = 10 dogs for AAG and AA and n = 6 dogs for G and S. *$P < .05$ *v* basal; †$P < .05$ *v* sedentary. Values with different letters at the corresponding time point are significantly different at $P < .05$. Positive and negative values refer to net uptake and net release, respectively.

Table 2. Cumulative Balance of Leu and Phe (μmol/kg/150 min) During Exercise Across the Hindlimb

Parameter	AAG	AA	G	S
Leu				
Hindlimb	27.6 ± 3.1[a]	25.0 ± 2.9[a]	0.6 ± 0.9[b]	1.3 ± 0.8[b]
Gut	66.3 ± 8.2[a]	51.9 ± 5.4[a]	−15.6 ± 2.0[b]	−17.6 ± 4.2[b]
Liver	25.4 ± 5.4[a]	26.1 ± 6.6[a]	−18.6 ± 3.1[b]	−27.4 ± 7.3[b]
Splanchnic	86.4 ± 10.1[a]	81.0 ± 8.9[a]	−37.6 ± 4.7[b]	−42.5 ± 6.9[b]
Phe				
Hindlimb	0.3 ± 0.9[a]	−1.3 ± 0.7[ab]	−1.7 ± 0.8[ab]	−2.9 ± 0.5[b]

NOTE. Data are the mean ± SE. Values with different letters are significantly different at $P < .05$ between treatments. See Table 1 for details.

The release was significant ($P < .05$) except for the late exercise period in the S treatment ($P = .054$).

The cumulative balance of Leu across the gut is shown in Table 2. The gut showed significant net uptake in the AAG and AA treatments ($P < .05$). The G and S treatments, on the other hand, showed significant net release of Leu ($P < .05$).

Hepatic Leu Balance

The liver showed a net release of Leu during the basal period in all treatments ($P < .05$). The balance in both the AAG and AA treatments showed a significant net uptake in the sedentary period. The uptake decreased slightly during the exercise period; however, it was still significantly different from the basal value. There was no significant difference between the AAG and AA treatments throughout the experiment. The liver continued to release Leu after initiating the infusion in the G and S treatments ($P < .05$), except for the late exercise period in the G treatment (Fig 2C).

The cumulative balance of Leu across the liver showed a net uptake in both the AAG and AA treatments ($P < .05$). Values did not differ between these treatments. The cumulative balance in the G and S treatments showed net release ($P < .05$) with no difference between the two treatments (Table 2).

Splanchnic Leu Balance

The splanchnic balance of Leu, that is, the sum of the balance of the gut and the liver, is presented in Fig 2D. In the basal period, all treatments showed a significant net release ($P < .05$). After initiating the infusion of AAG and AA solutions, the balance became positive; however, it showed a net release in the G and S treatments.

The cumulative Leu balance during the exercise period was positive in the AAG and AA treatments ($P < .05$); however, it was negative in the G and S treatments ($P < .05$). No significant difference existed between AAG and AA or between G and S (Table 2).

Hindlimb Phe Balance

Hindlimb Phe balance is shown in Fig 3. The balance showed net release in the basal period for all treatments ($P < .05$). The balance demonstrated a net uptake in the sedentary period for the AAG and AA treatments ($P < .05$), whereas it continued to show a net release in the G ($P = .09$) and S ($P < .05$) treatments. The net uptake observed in the AAG and AA treatments disappeared during the exercise period. The net release in the S treatment was significant during both the early and late exercise periods; however, it was significant only in the late exercise period in the G and AA treatments. No significant release was observed for the AAG treatment throughout the exercise period.

The cumulative balance of Phe during the exercise period demonstrated a significant net release in the S treatment and a tendency for release in the AA ($P = .096$) and G ($P = .07$) treatments, whereas the balance was not significantly different from zero in the AAG treatment. In addition, the balance differed significantly between the AAG and S treatments (Table 2).

DISCUSSION

Phe release from the hindlimb increased significantly during the early exercise period when S was infused, which thus indicated exercise-augmented skeletal muscle protein degradation. This result is consistent with previous findings.[1-4,15] On the other hand, the supplementation of AAG reduced the exercise-induced increase in Phe release from the hindlimb. We previously reported that supplementation of these nutrients achieves net protein synthesis during a recovery period after exercise.[15]

Insulin has been reported to stimulate skeletal muscle protein synthesis.[16,17] The increased availability of both insulin and AA enhanced protein synthesis further.[17-20] In the present study, during the sedentary period, hindlimb Phe net release turned to net uptake in both the AAG and AA treatments; however, plasma insulin levels were significantly higher for AAG versus AA. In the G treatment, plasma insulin increased during the sedentary period, but hindlimb Phe balance still demonstrated net release. These results suggest that the availability of AA had a greater impact on skeletal muscle protein synthesis than the availability of insulin during the resting state. On the other hand, during exercise, high concentrations of plasma AA were maintained in both the AAG and AA treatments. The cumulative balance of hindlimb Phe showed a tendency for release in the AA treatment ($P = .096$), whereas the balance did not differ from zero in the AAG treatment. Plasma AA concentrations

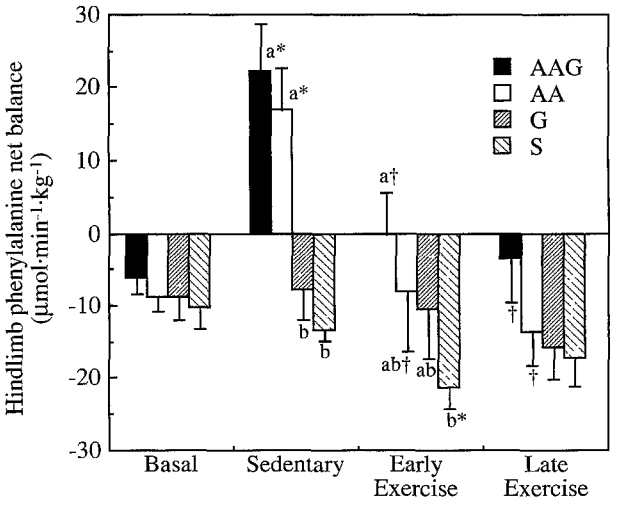

Fig 3. Hindlimb Phe balance. Data are the mean ± SE. See Fig 2 for details.

with AAG and AA treatments were comparable during the exercise period; however, plasma insulin levels were significantly higher for AAG versus AA. These results thus suggest that not only AA but also insulin may be required to stimulate skeletal muscle protein synthesis during exercise. A previous report showed that exercise is an essential factor for exerting a stimulatory effect of insulin on skeletal muscle protein synthesis,[21] and these findings also support our present findings.

It is noteworthy that administration of G alone did not decrease skeletal muscle protein breakdown induced by exercise. The exercise-induced increase of AA oxidation[11] and the increase in proteolysis[12] were both reduced by supplementation of carbohydrates. It thus seems that carbohydrate supplementation could decrease AA oxidation and skeletal muscle protein degradation during exercise; however, this regimen may not be able to abolish skeletal muscle protein breakdown completely. These findings suggest that AA may thus be necessary to achieve net skeletal muscle protein synthesis during exercise.

In the present study, the release of Leu from the gut increased during the exercise period in the S treatment. Since the animals were in a fasted state, the increase in release of an essential AA such as Leu from the gut indicates that proteolysis in this tissue was augmented. This finding is consistent with previous results reported by Wasserman et al.[6,15] One of the metabolic consequences of physical activity is a change in the distribution of the blood flow, namely from the splanchnic bed to the skeletal muscle,[22] which is considered to hasten gut proteolysis.[8] However, in the present study, the portal vein blood flow did not change during exercise. It thus does not seem that a reduction of blood flow across the gut triggered gut proteolysis in the present study. Hypoglycemia in the brain has been reported to induce gut proteolysis due to either the activation of adrenergic neurons or an increase in endorphins.[23-25] It is well known that exercise activates adrenergic neurons[26,27] and increases the plasma endorphin level.[28]

The net uptake of Leu in the gut during exercise was observed after the AAG and AA treatments. In addition, Leu uptake tended to be greater with AAG versus AA during the late exercise period ($P = .06$). However, the G treatment failed to achieve net uptake of Leu by the gut during exercise. These findings suggest that exercise-induced gut proteolysis may thus decrease after administration of AA, and this effect may be enhanced by concomitant supplementation of G. On the other hand, carbohydrate administration without AA did not effectively achieve net protein synthesis.

The arterial plasma Leu concentration was significantly lower with AAG versus AA. Leu uptake by the gut tended to be higher with AAG versus AA. These results suggest that the lower Leu level in the plasma appears to be associated, at least in part, with the higher uptake of the amino acid by the gut. We previously reported that during recovery after exercise, the arterial Phe level was significantly low when the uptake of Phe by the hindlimb was high, and the increased insulin sensitivity in skeletal muscle was thus suggested to be related to the higher uptake.[15] In the present study, plasma insulin was higher for AAG versus AA; however, the uptake of both Leu and Phe by the hindlimb was not significantly higher for AAG versus AA. Therefore, it may be reasonable to postulate that the increase in plasma insulin in the present study might not be large enough to exert a stimulatory effect of insulin on skeletal muscle AA uptake. Another plausible reason could be the differences in the physiological condition, since a previous study was performed during the recovery state and the current study was performed during exercise.

In conclusion, exercise was found to augment protein breakdown in both the skeletal muscle and the gut. Proteolysis occurring in the gut during exercise may thus be reduced by the supplementation of AA, and this effect may be enhanced by simultaneous G administration. In contrast, both AA and G might be required to abolish the net protein degradation during exercise in skeletal muscle. However, G without AA failed to achieve net protein synthesis in either the skeletal muscle or the gut.

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