Glycemic Carbohydrates Consumed with Amino Acids or Protein Right after Exercise Enhance Muscle Formation
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This review shows the importance of high–glycemic carbohydrates consumed together with protein in enhancing the exercise-induced muscle formation relative to timing of intake. Insulin, which increases in blood after glycemic carbohydrate ingestion, seems to effectively stimulate protein synthesis and inhibit protein degradation right after exercise rather than later. This presents a new aspect in nutrition: the importance of intake timing in addition to the composition and amount of nutrients.

Key words: protein, exercise-induced muscle formation, insulin

Introduction

Exercise is important in preventing disease and is beneficial and in both maintenance and improvement of health. Part of this exercise-related health benefit owes to the improvement of body composition, including reducing body fat and increasing skeletal muscle mass.

A reduction in lean body mass, which mainly consists of skeletal muscle, was reported to be a risk factor for increasing body weight or body fat in later life. Because the resting metabolic rate accounts for 60 to 75% of daily energy expenditure, even a small increase in the rate could reduce the amount of energy accumulated as body fat. Skeletal muscle is a major determinant of resting metabolic rate, such that maintaining or increasing the skeletal muscle mass is one of the keys to preventing increased body fat and ultimately obesity.

Total skeletal muscle mass declines with aging; this muscle atrophy is accompanied by a reduction in muscle strength and marks the development of sarcopenia. The age-related changes in muscle mass and function lead to a reduction in performance, increased risk for falls, and increased vulnerability to injury, especially bone fracture. Furthermore, a decrease in muscle function can lead to reduced physical activity, which may have metabolic effects including decreased bone density, obesity, and impaired glucose tolerance.

Exercise training is essential for skeletal muscle accretion. Because protein is the predominant constituent of skeletal muscle, dietary protein is regarded as another important factor in building skeletal muscle. Previous studies have demonstrated that increasing protein intake to 1.6 g \( kg^{-1} \) \( day^{-1} \), approximately double the recommended dietary allowance of protein in the United States, in combination with resistance training, is beneficial for increasing skeletal muscle protein synthesis. However, increasing protein intake alone without exercise did not have this effect.

Suzuki et al. examined the effects of the timing of nutrient administration on lipid and carbohydrate metabolism in rats after exercise. Ivy et al. also reported that in men the skeletal muscle showed a significantly higher glycogen recovery when a glycemic carbohydrate, glucose, was ingested immediately after exercise than when ingested two hours after exercise. These findings suggest that the same would be true of the relationships between nutritional intakes and exercise-induced muscle formation.

Exercise is known to alter the individual components of muscle protein homeostasis. During exercise, net catabolism of protein is enhanced, observed as amino acid oxidation, and rates of skeletal muscle protein synthesis are reduced. Exercise also has been shown to accelerate rates of proteolysis with myofibrillar protein. During the recovery phase after exercise, net protein homeostasis rebounds as myofibrillar protein rates are increased and as amino acid oxidation is diminished. Skeletal muscle protein synthesis has been demonstrated to increase after both resistance and moderate-intensity aerobic exercise. However, there are limited data demonstrating the effect of timing of nutrient administration on protein metabolism.

Although several mechanisms are responsible for the improved glycogen recovery with earlier intake of...
glycemic carbohydrate after exercise,7 the interaction between exercise and insulin release associated with a glycemic carbohydrate load is considered very important. One may therefore hypothesize that earlier consumption of protein after exercise may be more effective at promoting muscle protein synthesis than later consumption. Insulin is critical in the regulation of protein synthesis, and the combination of elevated insulin and amino acid supplementation stimulates protein synthesis.12–14

A series of studies were conducted to determine whether increased amino acid and insulin availability after exercise alters protein kinetics in the dog, rat, and human.

Early Feeding of Amino Acids Mixed with Glucose after Exercise Promotes Muscle Protein Accretion to a Greater Extent than Later Feeding

Acute Study in Dogs Loaded after Treadmill Running

The first study was conducted to investigate whether feeding amino acids and glycemic carbohydrate (i.e., glucose) in the early phase of a recovery period after exercise was more effective in promoting skeletal muscle accretion than later feeding. Okamura et al. measured the rate of muscle protein synthesis and degradation in dogs that were administered amino acids and glucose at different times after exercise.15 The dogs ran on a treadmill for 150 minutes at a moderate speed (10 km/hour, 12% incline). After the exercise, half of them (right after group = R) had a 2-hour infusion of a 10% amino acid solution (18 amino acids, Amiparen, Otsuka Pharmaceutical, Tokyo, and a 10% glucose solution) into the portal vein, whereas the other half were infused with the solution starting 2 hours after the exercise and continuing for 2 hours (later group = L). Each dog was subjected to both infusion regimens, R and L, and the order of the treatment was randomized. Each study was separated by at least 2 weeks. The rate of skeletal muscle protein synthesis and degradation was measured based on the net balance of an amino acid, phenylalanine (Phe), across the hindlimb along with the measurement of the dilution of stable isotope [2H5]Phe.16 The net balance of Phe across the hindlimb was calculated by multiplying the arteriovenous difference of the Phe concentration by the blood flow across the hindlimb. Because Phe itself is not metabolized within the skeletal muscle, the release of the amino acid indicates the net degradation that occurs in muscle, and the uptake indicates the net synthesis.

During the pre-exercise period, the balance showed a net release (net protein breakdown), and the net release was sustained throughout the exercise period with no difference between the groups. In R, the balance of Phe changed to a net uptake (net protein synthesis) after initiating the infusion of the test solution immediately after exercise. On the other hand, in L during the first 2 hours of the recovery period when saline was infused, the balance remained at the net protein breakdown, whereas the balance changed to a net uptake after initiating the infusion of the test solution.

An interesting finding was that the uptake of Phe during the test solution infusion period tended to be higher in R than in L. The uptake during the last half of the infusion period was significantly higher in R than in L. These findings demonstrate that the earlier administration of amino acids and the glycemic carbohydrate, after exercise enhanced the net incorporation of Phe into muscle protein to a greater extent than later administration of the same nutrients; from this one might conclude that there is an enhanced synthesis of skeletal muscle protein with early administration of amino acids and glycemic carbohydrate.

The rates of muscle protein synthesis and degradation during nutrient infusion are shown in Table 1. The synthesis rate was found to be significantly higher in R than in L (29.7 ± 9.6 vs. 22.0 ± 10.1 nmol · kg⁻¹ · min⁻¹, P < 0.05), whereas the rate of proteolysis did not differ between R and L. As a result, net muscle protein synthesis was significantly higher in R than in L (10.9 ± 6.6 vs. 4.8 ± 2.8 nmol · kg⁻¹ · min⁻¹, P < 0.05). These findings suggest that the early intake of amino acids and the glycemic carbohydrate after exercise may be more effective for increasing muscle protein accretion than a later intake of these same nutrients.

Gautsch et al. recently demonstrated that a complete meal, including both protein and glycemic carbohydrates, is needed to stimulate mRNA translation initiation for muscle protein synthesis.17 However, carbohydrate alone did not have the effect. In another study,
Hamada et al. showed that glucose administered together with amino acids gave lower hepatic urea release and urinary urea excretion compared with when amino acids alone were supplied. These results suggest that glucose may stimulate insulin secretion and facilitate the incorporation of ingested amino acids into body protein. Thus, not only protein but also insulinogenic and glycemic carbohydrates are important to promote muscle protein synthesis. These findings support the concept that intake of nutrients other than amino acids or protein is necessary to achieve exercise-induced muscle protein accretion. Furthermore, earlier intake will produce more effective muscle protein synthesis. Although the mechanisms responsible for the consumption timing effects cannot be completely defined from the results obtained from the dog study, we noted that plasma insulin levels during the test solution infusions were significantly lower in R than in L. Insulin is known to increase protein synthesis and to decrease protein breakdown, resulting in decreased amino acid levels in plasma and muscle cells. In the dog study, although arterial insulin levels were lower in R than in L, amino acid concentrations were also lower in R (0–120 minutes) than in L (120–240 minutes) (4525 ± 381 vs. 5241 ± 673 nmol/mL, P <0.001). Protein synthesis was greater in R than in L. Together, these data suggest that muscle protein metabolism is more responsive to insulin earlier in the recovery period. Thus it seems a reasonable hypothesis that, if the plasma insulin levels were comparable in R and L, the increases in hindlimb amino acid uptake and protein synthesis for R versus L may have been greater.

**Chronic Study in Rats with Resistance Exercise Training**

The previous dog study suggested that increasing plasma insulin by administering high–glycemic carbohydrate with amino acids may enhance the beneficial effect of amino acids on skeletal muscle protein synthesis. We therefore compared the anabolic effects of chronic feeding of high insulinogenic and glycemic glucose or sucrose and low insulinogenic and glycemic fructose or erythritol together with amino acids right after resistance exercise on skeletal muscle mass in rats.

**Sucrose versus fructose.** Male Sprague-Dawley rats were meal-fed twice a day (11–12 hour and 19–20 hour) and one-half of the rats were loaded with squat exercise at 6 to 7 am, every other day. At 7 am on the exercise day, all rats were orally (gastric tube) fed the solution containing the amino acid mixture (10% amino acids solution, 10 mL/kg) together with sucrose or fructose (5.4 mmol/kg). After 8 weeks the rats were killed to obtain adipose tissues and leg skeletal muscles. Body weights and adipose tissue weights (% of body weight) were significantly lower in the training groups than in the sedentary groups of either sucrose- or fructose-fed rats. Furthermore, they were not significantly different between fructose- and sucrose-fed groups with or without training. Interestingly, gastrocnemius and quadriceps muscle mass (% of body weight) were significantly higher in the training group than in the sedentary group in sucrose-fed rats, but not significantly different between training and sedentary groups in the fructose-fed rats. The two skeletal muscle weights were not significantly different between fructose- and sucrose-fed groups with or without resistance training. These results suggest that high-insulinogenic and high-glycemic carbohydrates could enhance exercise-induced muscle accretion.

**Glucose versus erythritol.** Experimental conditions were almost the same with the sucrose versus fructose study, but the rats were orally fed a solution containing an amino acid mixture (AA) alone or together with the high-insulinogenic and low-glycemic glucose or low-insulinogenic and low-glycemic sweetener, erythritol (BOLATOL-E, Mitsui Sugar Co. Ltd., Tokyo) at a dosage of 5.4 mmol/kg.

After 8 weeks of the experiment, 24-hour urine was collected for the analysis of 3-methyl-histidine and creatinine. On the exercise day, blood was obtained from the tail vein at –60, 0, 10, 20, 30, 40, 60, 120, 240 and 480 minutes after the oral administration of the amino acid mixture and sugar for the analysis of plasma glucose and insulin.

Body weights were not significantly different between glucose with AA, erythritol with AA, and AA groups in either sedentary rats or training rats. Body weights in training groups were significantly lower than those in sedentary groups, however, but no effects of nutritional treatment were found. Adipose tissue weights were not significantly different between glucose with AA, erythritol with AA, and AA groups in either sedentary rats or in training rats. Adipose tissue weights in training groups fed AA or erythritol with AA were significantly lower than in their sedentary counterparts.

Quadriceps muscle mass (% of body weight) was not significantly different between glucose with AA, erythritol with AA, and AA groups in either sedentary rats or training rats. However, quadriceps muscle mass of the training group fed with glucose and AA was significantly greater than those of three sedentary groups. Total weights of seven skeletal muscles were not significantly different between glucose with AA, erythritol with AA, and AA groups in either sedentary or training rats. Training groups had significantly greater total muscle weights than their sedentary counterparts; the training group fed glucose with AA showed a significantly greater total muscle weight than the sedentary groups fed erythritol with AA or AA.
Protein contents of quadriceps muscle were not significantly different between glucose with AA, erythritol with AA, and AA groups in sedentary rats; however, in training rats they were significantly higher in the group receiving glucose with AA than in groups receiving either erythritol with AA or AA alone. Total muscle protein contents were not significantly different between glucose with AA, erythritol with AA, and AA groups in either sedentary rats or training rats; however, total muscle protein contents of the training groups were significantly greater than their sedentary counterparts.

Urinary 3-methyl histidine–to–creatinine ratio was not significantly different between groups receiving glucose with AA than in the groups receiving erythritol with AA, and AA groups in sedentary rats. In training rats, however, it was significantly lower in the group receiving glucose with AA than in the groups receiving erythritol with AA and AA alone. There were no significant differences in urinary 3-methyl histidine between sedentary groups.

Plasma glucose responses to receiving amino acid together with sugars were significantly higher in the group receiving glucose with AA than in the group receiving erythritol with AA and in the groups receiving AA that were either sedentary or training for 120 minutes after the feeding. Plasma insulin responses were also significantly higher in the group receiving glucose with AA than in the group receiving erythritol with AA, the groups receiving AA for the initial 30 minutes in sedentary rats, and the group receiving AA for initial 60 minutes in training rats.

Training rats had smaller and fewer adipose tissues, larger muscles, and more muscle protein; high-insulinogenic and high-glycemic carbohydrate (i.e., sucrose) taken together with an amino acid mixture enhanced resistance training–induced protein accretion in skeletal muscle, and lowered the skeletal muscle breakdown by increasing plasma glucose and insulin levels during the recovery period after resistance exercise.

These results indicate positive effects of the high-insulinogenic and high-glycemic sugars such as glucose and sucrose fed together with an amino acid mixture right after exercise on skeletal muscle formation compared with feeding low-insulinogenic and low-glycemic sugars such as fructose and erythritol. In the skeletal muscle, high-insulinogenic sugar feeding might effectively up-regulate the muscle protein synthesis when the protein and amino acids were fed directly after exercise. This effect may be due to the interaction between increased insulin sensitivity in skeletal muscle right after exercise and increased blood insulin level from being fed high-insulinogenic sugars such as glucose and sucrose.

Recent adult human studies investigated the effects of ingesting a bolus of 6 g of eight essential amino acids combined with 35 g of high-insulinogenic carbohydrate (i.e., sucrose) immediately before and after, or 0, 1, and 3 hours after, resistance exercise (10×8 leg press and leg extension at 80% of one repetition maximum) on muscle protein anabolism. In addition, the response of net protein synthesis to consumption of the supplement immediately before resistance exercise was significantly greater than the response when the supplement was consumed after exercise, primarily because of an increase in muscle protein synthesis as a result of increased delivery of amino acids to the leg. These results suggest that the combination of increased amino acid levels at a time when blood flow was increased appears to offer the maximum stimulation of muscle protein synthesis by increasing amino acid delivery to the muscle and, therefore, amino acid availability.

**Early Feeding of Protein Mixed with Glycemic Carbohydrate Supplement after Exercise Promotes Muscle Protein Accretion**

**Acute Study in Humans with Bicycle Ergometer Exercise**

Findings from the dog study were almost completely confirmed with a human study. Levenhagen et al. fed a supplement of protein mixed with high-insulinogenic and high-glycemic carbohydrate (i.e., sucrose) to 10 adult subjects (5 males and 5 females, aged 20–41 years, and within 25% of ideal body weight) immediately (R) or 3 hours (L) after 60 minutes of moderate-intensity exercise (stationary cycle exercise). The supplement contained 10 g protein, 8 g carbohydrate, and 3 g fat (Jogg Mate Protein, Otsuka Pharmaceutical, Tokyo). Leg blood flow and circulating concentrations of glucose, amino acids, and insulin were similar for R and L. Leg glucose uptake and whole-body glucose utilization were enhanced or increased threefold and 44%, respectively, for R versus L. Although essential and nonessential amino acids were taken up by the leg in R, they were released in L. Although proteolysis was unaffected, leg and whole-body protein synthesis were elevated threefold and 12%, respectively, for R versus L, resulting in a net gain of leg and whole-body protein. Therefore, similar to carbohydrate homeostasis, R post-exercise ingestion of a protein and high-insulinogenic and high-glycemic carbohydrate supplement enhances accretion of whole-body and skeletal muscle protein. The early post-exercise ingestion of a supplement containing protein and high-insulinogenic and high-glycemic carbohydrate enhances accretion of whole-body and skeletal muscle protein, suggesting a common mechanism of exercise-induced insulin action as stimulating glucose and amino acid transport.
Chronic Study in Adult Humans under Conditions of Dieting and Light Resistance Exercise

Based on the findings obtained from dogs, rats, and humans, a human study carried out to confirm the findings could be applied to dieting humans.26

Fifteen moderately obese female subjects volunteered for a 12-week trial. The subjects were randomly assigned to a group that ingested a supplement consisting of protein mixed with glycemic carbohydrate (i.e., sucrose, Jogg Mate Protein)25 immediately after light resistance training (body mass index [BMI, kg/m²] 25.6 ± 1.8, n = 7) or to a group that did not ingest any supplement after exercise (BMI = 26.2 ± 3.7, n = 8). In both groups, energy consumption during the study was restricted to 85% of energy requirement. The subjects performed a light resistance exercise training program using lightweight dumb-bells (2–3 kg) every day from hour 1700 to 1730. The dumb-bell exercise program consisted of 12 types of exercise, in which whole-body muscles were used. The supper was served to all subjects at hour 1900. The energy and protein intake was similar in the two groups throughout the study. Body composition and resting metabolic rate were measured before and after the 12-week study.

Body weights decreased in both groups after the 12-week study. The decrease was greater in the supplement-fed group than in control, but there was no statistically significant difference between the groups. Fat mass decreased significantly in both groups. Again, this was greater in the supplement-fed group than in the control group, but no significant difference between the groups was observed. On the other hand, lean body mass increased in the supplement-fed group, whereas the control group showed no change in lean body mass. The resting metabolic rate and post-meal total energy output significantly increased in the supplement-fed group, whereas these variables did not change in the control group.

These results suggest that the ingestion of the protein and high-glycemic carbohydrate supplement immediately after exercise may be more effective for reducing body fat and increasing muscle mass.

Chronic Study in Elderly with Resistance Training

Aging is associated with a progressive reduction of skeletal muscle volume27 and a concomitant reduction in strength.28–31 This influences physical performance and thereby the daily function of the elderly. However, resistance training has been shown to counteract the atrophy and loss of strength in this age group.32–35

Esmarck et al.36 investigated the effect of the timing of a supplement containing protein and carbohydrate after exercise on the development of muscle hypertrophy and strength during a period of resistance training in elderly individuals. Muscle hypertrophy was evaluated by magnetic resonance imaging and from muscle biopsy samples, and muscle strength was determined using both dynamic and isokinetic strength measurements. The acute glucose, insulin, and catecholamine responses to exercise and supplementation were also determined 4 hours after training.

Thirteen men (aged 74 ± 1, BMI 25 ± 1) completed a 12-week resistance training program (3 times per week) while receiving a supplement containing protein mixed with glycemic carbohydrate (Jog Mate Protein25) immediately after (R) or 2 hours after (L) each training session. Body composition was determined by dual-X-ray absorptiometry and food records were obtained over 4 days.

In response to training, the cross-sectional area of muscle quadriceps femoris and mean fiber area increased in the R group, whereas no significant increase was observed in the L group. For the R group both dynamic and isokinetic strength increased, by 46 and 15%, respectively (P <0.05), whereas the L group only improved in dynamic strength, by 36% (P <0.05). No differences in glucose or insulin response were observed between protein and glycemic carbohydrate supplement intake at 0 and 2 hours post-exercise. In this study muscle hypertrophy was more pronounced in the R group than in the L group despite identical rises in plasma insulin after intake of a supplement containing protein and carbohydrate. However, it may be speculated as to whether the insulin sensitivity of protein turnover is markedly higher immediately after exercise than 2 hours later as suggested in the dog study.15

This study investigated the importance of the timing of protein and high-glycemic carbohydrate intake after each exercise bout over 12 weeks of resistance training on morphologic and strength characteristics of skeletal muscle in elderly individuals.

Ingesting a Meal Soon after Exercise over a Long Period of Time Is Effective in Increasing Muscle Mass and Reducing Body Fat

The next study was conducted in rats to elucidate whether having a meal containing glycemic carbohydrates and protein soon after exercise promotes muscle protein accretion to a greater extent than ingesting a meal several hours later.37

Twenty male Sprague-Dawley rats, which were meal-fed twice a day, were randomly assigned either to a group that received the post-exercise meal (rat chow diet) right after exercise (R group, n = 10) or to a group receiving their meals 4 hours after exercise (L group, n = 10). The rats underwent resistance exercise from hour 0600 to hour 0700, three times a week for 10
weeks using previously described resistance exercise (i.e., squatting) equipment designed for rats. The rats in R were fed meals from hour 0700 to hour 0800 and from hour 1900 to hour 2000, whereas the rats in L were fed from hour 1100 to hour 1200 and from hour 1900 to hour 2000 under 12-hour light (0700–1900) and dark cycle.

Body weight gain during the study period was similar for the two groups; the final weights were not different between R and L (R = 484 ± 5 g and L = 477 ± 8 g). The total weights of the skeletal muscle samples (i.e., triceps brachi, soleus, extensor digitorum longs, plantaris, tibialis anterio, gastrocnemius, and quadriceps femoris) were significantly higher in R than in L (14.9 ± 0.8 vs. 14.1 ± 1.0 g, P <0.05), whereas both the weight of each and the total weights of abdominal adipose tissues (i.e., epididymal, perirenal, and mesenteric) were significantly lower in R than in L (21.1 ± 4.1 vs. 27.7 ± 7.1 g, P <0.01).

The lipoprotein lipase (LPL) activities in the heart and the soleus muscle were significantly higher in R than in L (heart 28.3 ± 4.7 vs. 22.5 ± 3.2 U/g, P <0.001; soleus 11.7 ± 2.2 vs. 6.6 ± 2.5 U/g, P <0.01). However, LPL activity in the epididymal adipose tissue did not differ between the groups. Because LPL catalyses the uptake of blood triacylglycerols into tissues, including skeletal muscle, the muscle tissues in R would take up a larger amount of triacylglycerols than those in L. This partition could contribute to the lower adipose tissue accumulation in R than in L after 10 weeks. Another possible mechanism underlying the lower fat deposition in R than in L could be the higher resting metabolic rate, which might be related to the larger skeletal muscle mass found in R than in L.

Because rats are nocturnal animals, the exercise training that was conducted in this study was the equivalent of late afternoon exercise for humans and the meal taken after exercise was equivalent to supper in humans. The present observations therefore indicate that having a meal following late afternoon exercise as soon as possible might be beneficial in reducing body fat and/or increasing skeletal muscle mass.

Conclusion

The above findings obtained from a series of studies showed that feeding amino acids or protein together with high-insulinogenic and high-glycemic carbohydrates and the feeding of mixed meals after exercise are essential to achieve net skeletal muscle protein. In addition, the earlier these nutrients or mixed meals were supplied, the greater the muscle protein synthesis rate was augmented. These findings also suggested that the regular ingestion of meals or a protein and carbohydrate supplement immediately after exercise over a long period of time might be effective for increasing lean body mass and decreasing body fat accumulation. Therefore, the timing of nutrition consumption after exercise appears to play an important role in maximizing the effect of an exercise and nutrition regimen.

As to the nutritional significance of glycemic carbohydrates, high-glycemic and high-insulinogenic carbohydrates are more effective than low-glycemic and low-insulinogenic carbohydrates for skeletal muscle formation. A combination of amino acids/protein, to increase amino acid availability, and high-glycemic carbohydrate, to stimulate insulin release, should be a potent stimulator of net muscle protein synthesis. In addition, the recovery of skeletal muscle glycogen after exercise was significantly greater when a high-glycemic carbohydrate (i.e., dextrin) was fed than when a low-glycemic carbohydrate (i.e., starch) was fed in rats. Some caution is needed in view of the recent trend to emphasize low-glycemic and low-insulinogenic carbohydrates for health in an effort to prevent and treat obesity, diabetes mellitus, and hyperlipidemia.


