REVIEW ARTICLE

Use of Amino Acids as Growth Hormone-Releasing Agents by Athletes

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Specific amino acids, such as arginine, lysine and ornithine, can stimulate growth hormone (GH) release when infused intravenously or administered orally. Many individuals consume amino acids before strength training workouts, believing this practice accentuates the exercise-induced GH release, thereby promoting greater gains in muscle mass and strength. The GH response to amino acid administration has a high degree of interindividual variability and may be altered by training status, sex, age, and diet. Although parenteral administration consistently leads to increased circulating GH concentration, oral doses that are great enough to induce significant GH release are likely to cause stomach discomfort and diarrhea. During exercise, intensity is a major determinant of GH release. Although one study showed that arginine infusion can heighten the GH response to exercise, no studies found that pre-exercise oral amino acid supplementation augments GH release. Further, no appropriately conducted scientific studies found that oral supplementation with amino acids, which are capable of inducing GH release, before strength training increases muscle mass and strength to a greater extent than strength training alone. The use of specific amino acids to stimulate GH release by athletes is not recommended. *Nutrition* 2002;18:657–661. ©Elsevier Science Inc. 2002

KEY WORDS: resistance exercise, strength training, muscle, arginine, lysine, ornithine

INTRODUCTION

Many athletes use specific amino acids to stimulate growth hormone (GH) secretion, believing that this practice will promote greater gains in muscle mass and strength than strength training alone. Exercise, including strength training exercise, also increases circulating GH concentrations. Amino acids may be used before a workout in an attempt to further accentuate the exercise-induced GH release.

The use of protein or specific amino acids to induce GH release apparently originated with the use of arginine infusion[1] and orally administered protein drinks such as Bovril[2] as diagnostic tests for GH secretion. Intravenous infusion of 183 mg of arginine per kilogram of body weight increased plasma GH over 20-fold in females,[3] and infusion of 30 g of arginine elevated serum GH concentrations 8.6-fold in males.[4] Arginine increases GH release by suppressing endogenous somatostatin secretion.[4] Infusion of other amino acids, including methionine, phenylalanine, lysine, and histidine, also promoted relatively large increases (~8- to 22-fold) in circulating GH levels.[5] Intravenous administration of ornithine also stimulated GH release.[6] Not all amino acids are effective GH-releasing agents when administered orally or intravenously. The branched-chain amino acids (BCAAs) leucine and valine induced rather small (~10%) increases in GH levels, whereas isoleucine did not affect GH release.[5] Ingestion of 10 g of aspartic acid, glutamic acid, or cysteine did not alter serum GH concentrations.[7] The most commonly studied primary and secondary amino acids for their effect on GH release, and possibly the most widely used, are arginine, lysine, and ornithine. This article examines the use of amino acids by athletes for the purpose of stimulating GH release.

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EFFECT OF AMINO ACID ADMINISTRATION ON GH RELEASE

Ingestion of 1.5 g of arginine plus 1.5 g of lysine by young adults increased plasma GH concentrations 2.7-fold at 60 min postconsumption, although GH levels were not elevated 30 or 90 min after ingestion[8] (Table I). Ingestion of 1.2 g of arginine plus 1.2 g of lysine by young males increased plasma GH concentrations within 30 min, and peak GH concentrations were nearly eight-fold greater 90 min after ingestion.[9] Either 1.2 or 2.4 g of arginine or 1.2 g of lysine alone had little effect on plasma GH concentrations. Two grams of glutamine increased plasma GH concentration 4.3-fold in 32- to 64-y-old individuals 90 min after ingestion.[10] It is unknown whether glutamine directly affected GH release or acted indirectly through conversion to arginine. Orally administered arginine plus lysine or glutamine can increase circulating GH concentrations, but other amino acids may not increase GH release.

Various factors including training status, sex, diet, time since last meal, and age appear to modify the GH response to amino acid and protein administration. The GH response to amino acid ingestion may be reduced in exercise-trained individuals. Consumption of a total of 2.4 g of arginine and lysine or 1.85 g of ornithine and tyrosine did not induce a statistically significant increase in serum GH concentrations over a 3-h period in young, male bodybuilders after an overnight fast.[11] GH concentrations increased in five of the seven subjects, and a large intersubject variability in GH concentrations was noted. For the 3-h period after arginine and lysine administration, there was a 26-fold difference in integrated GH concentrations between subjects with the lowest and highest GH concentrations. This may be explained in part by the pulsatile release pattern of GH.

Larger amounts of amino acids may be necessary to elicit GH release in exercise-trained adults. Nine male and three female bodybuilders ingested 40, 100, and 170 mg/kg of ornithine after an overnight fast on three separate occasions.[12] These dosages are

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TABLE I.

EFFECT OF AMINO ACIDS ON GROWTH HORMONE RELEASE

Reference	Subject age (y)*	Sex	Fitness/training status	Amino acids and dosages	Oral/IV	Growth hormone response
Carlson et al.[7]	23–32	Male and female	Normal, non-obese	10 g asp, or gln, or cys	Oral	No effect
Suminski et al.[8]	22.4 ± 0.8	Male and female	Resistance training, 2–3 d/wk	1.5 g arg + 1.5 g lys	Oral	↑ 2.7-fold at 60 min
Isidori et al.[9]	15–20	Males	"Healthy"	1.2 g lys	Oral	No effect
				1.2 g or 2.4 g arg	Oral	No effect
				1.2 g arg + 1.2 g lys	Oral	↑ 8-fold at 90 min
Welbourne[10]	32–64	Male and female	"Healthy" (BMI = 25.6 ± 1.5	2.0 g gln	Oral	↑ 4.3-fold at 90 min
Lambert et al.[11]	22.6 ± 1.0	Male	Bodybuilders	2.4 g arg + 2.4 g lys	Oral	No effect
				1.85 g orn + tyr	Oral	No effect
Bucci et al.[12]	28.1 (male) 34.3 (female)	Male and female	Bodybuilders	40, 100, 170 mg/kg orn	Oral	No effect at 40, 100 mg/kg ↑ ~4-fold at 170 mg/kg
Merimee et al.[3]	17–35	Male and female	"Healthy"	183 mg arg/kg	IV	Females ↑; males, no change
				367 mg arg/kg	IV	Female ↑, males ↑; females > males
				550 mg arg/kg	IV	Females ↑, males ↑; female > males
Tanaka et al.[13]	17.2 ± 1.0	Male and female	BMI = 34.7 ± 1.9	0.5 g arg/kg	IV	↑ ≈13-fold
	25.3 ± 0.9	Male and female	BMI = 35.6 ± 1.3	0.5 g arg/kg	IV	↑ ≈7-fold
	50.4 ± 3.4	Male and female	BMI = 35.5 ± 2.1	0.5 g arg/kg	IV	↑ ≈6-fold
Corpas et al.[14]	69 ± 5	Male	Normal, non-obese	3.0 g arg + 3.0 g lys, twice daily for 14 d	Oral	No effect

* Data are presented as mean ± standard deviation or range.
arg, arginine; asp, asparagine; BMI, body mass index (mean ± standard deviation); cys, cysteine; gln, glutamine; IV, intravenous; lys, lysine; orn, ornithine.

approximately 3, 7, and 12 g for a 70-kg reference man and approximately 2.3, 5.7, and 9.6 g for a 56-kg reference woman. Ninety minutes after administration of the 170-mg/kg dose, mean serum GH concentration increased approximately four-fold, but GH levels were not altered by the 40- or 100-mg/kg doses. However, at the highest dose all subjects experienced mild to severe stomach cramping and diarrhea.[12]

Females have more consistent and greater increases in GH concentrations than males in response to amino acid use.[3] Intravenous administration of 183 mg/kg of body weight of arginine significantly increased plasma GH concentrations in females, age 17 to 35 y, after 60 min but not in males of similar age.[3] A dosage of 367 mg/kg was necessary for elevating GH levels in the males. At dosages of 367 mg/kg and 550 mg/kg, the increases in GH concentration were substantially greater in females than in males. Further, females showed less variability in the GH response to arginine. Ninety-seven percent of females infused with 367 or 550 mg/kg had increases in plasma GH concentration of 5.0 μg/mL or greater, but only 56% of males had increases of similar magnitude at these dosages. These results are consistent with the stimulation of GH release in all women, but only 20% of men, who consumed Bovril.[2] Bovril contains 7.8 g of protein, including 438 mg of arginine and 412 mg of lysine. The elevation in plasma GH levels in response to arginine infusion was more than doubled in males pretreated with the estrogen receptor agonist, stilbestrol, suggesting that the greater GH release in females is due to enhancement of GH release by estrogen.[3]

The magnitude of the GH response to specific amino acids is accentuated in young subjects. Arginine infusion stimulated GH secretion in 100% of subjects aged 16 to 19 y, but only 44% of the subjects aged 20 to 29 y, and 18% of subjects aged 30 to 71 y.[13] Only 50% of subjects aged 20 to 25 y had increases in GH levels after consumption of 1.5 g of arginine plus 1.5 g of lysine.[7] Consumption of 3 g of arginine plus 3 g of lysine twice daily for 14 d did not significantly alter GH levels in elderly subjects.[14] Younger individuals demonstrate a more robust GH response than do middle-aged and elderly subjects.

The acute GH response to amino acid ingestion may be influenced by the amount of dietary protein or amino acid consumption. Amino acid ingestion did not significantly affect GH release in male weight lifters who were consuming 1.58 $g \cdot kg^{-1} d^{-1}$ [11] or 2.2 $g \cdot kg^{-1} d^{-1}$ [15] of protein. The use of specific amino acids to induce GH release may not be very effective in strength-trained individuals consuming high-protein diets. Diets high in protein apparently increase basal GH levels.[16] The apparent reduction in GH release in male bodybuilders may be due in part to consumption of large quantities of protein or amino acids and high basal GH levels.[11]

In addition, the timing of amino acid ingestion relative to food consumption is likely to affect the GH response. Relatively low blood glucose levels, such as after a fast or consumption of a low-carbohydrate diet, appear to accentuate the effects of pharmacologic or physiologic stimulation of GH secretion.[17,18] However, from a practical perspective, the benefits of regular food consumption likely outweigh any benefits of attempting to enhance an amino acid or exercise-induced GH response by fasting. Food intake affects whole-body and tissue protein turnover.[19] After food ingestion, net whole-body protein deposition occurs due largely to an increase in protein synthesis. During fasting, rates of whole-body protein synthesis are lower than protein degradation rates.[19] Also, consumption of a supplement containing essential amino acids and carbohydrate before resistance exercise resulted in a greater protein synthesis response compared with consumption postexercise.[20]

EXERCISE-INDUCED ALTERATIONS IN CIRCULATING GH LEVELS

GH release during aerobic exercise is clearly related to exercise intensity[21,22] and duration.[23] GH increases during resistance exercise also appear to be positively related to intensity and volume (number of sets and repetitions) and inversely related to the length of the rest periods between sets.[24–28] For example, GH concentrations increased approximately 10-fold during three sets of 10 repetitions with a 10–repetition maximum (RM) load and remained elevated to 35 min postexercise.[29] Performing vertical leg lifts at 85% of 1 RM increased circulating GH concentration, but the same exercise at 28% of 1 RM did not affect GH levels.[28] However, there was no difference in the GH response to lower body resistance exercises when a resistance of 70% of 3 and 6 RM (depending on the exercise) was compared with 100% of 3 and 6 RM.[30]

Although the GH response to amino acids is affected by sex and training status, these factors have little effect on the exercise-induced GH response. Males and females show GH responses of similar magnitude to aerobic[31,32] and strength-training exercise,[26] especially if exercise intensity and duration are sufficient. In some reports, relative increases were larger in the males due to greater resting levels in the females.[31] The only notable difference between men and women appears to be that females achieve peak GH levels during exercise more quickly than males.[31,32] Aerobic exercise training reduced the GH response to a single bout of cycling exercise at the same absolute power output,[33] but differences between untrained and trained individuals were less clear when tested at the same relative intensity.[31,34] Women with at least 1 y of weight-training experience had a greater integrated GH response than did untrained women as a result of an acute bout of resistance training exercise with 10-RM resistance.[35]

It is apparent that exercise is a potent stimulus for GH release. Cycling at approximately 75% to 90% of maximum oxygen consumption for 20 min resulted in an approximately three-fold greater increase in GH concentrations compared with infusion of 30 g of arginine.[23] Because high-intensity aerobic or resistance training exercise are potent stimuli for GH release, ingestion of specific amino acids before exercise might not elevate GH levels further.

EXERCISE AND AMINO ACIDS

GH levels were elevated dramatically during a strength-training workout in experienced weight lifters and remained higher for approximately 70 min postexercise.[8] Subjects performed three sets to voluntary exhaustion at 70% of their 1 RM for seven different exercises. Although GH concentrations increased 2.7-fold after consumption of 1.5 g of arginine plus 1.5 g of ornithine, amino acid ingestion before the workout did not result in greater increases in GH concentrations than exercise alone[8] (Table II). Blood GH concentration was elevated in five male throwers 2 h after a weight-training circuit, which was performed after an overnight fast.[36] Consumption of an amino acid combination of 1.8 g of arginine, 1.2 g of ornithine, 0.48 g of methionine, and 0.12 g of phenylalanine did not enhance GH release during the workout. Exercise is a potent stimulus for GH release; therefore, amino acids might not enhance GH release during or after exercise.

Amino acid consumption over several days does not appear to alter GH levels in highly trained weight lifters.[15,37] Consumption of a total of 3 g of arginine, lysine, and ornithine before a 90-min weightlifting session and again before sleeping over a 4-d period did not alter the pattern and magnitude of GH secretion over 24 h in highly trained weight lifters.[15] Subjects consumed high-protein

TABLE II.

EFFECT OF AMINO ACIDS AND EXERCISE ON GROWTH HORMONE RELEASE

Reference	Subject age (y)*	Sex	Fitness/training status	Exercise	Amino Acids and Dosages	Oral/IV	Growth Hormone Response
Suminski et al.[8]	22.4 ± 0.8	Male	Resistance training, 2–3 d/wk	3 sets to failure, 70% 1 RM, 7 exercises	1.5 g arg + 1.5 g lys	Oral	Exercise ↑ GH; AA ↑ GH; AA did not increase exercise-induced GH release
Fogelholm et al.[15]	19–35	Male	Highly trained weight lifters	90 min weight lifting; 70–80% 1RM	6 g arg, lys, orn, daily for 6 d	Oral	No difference placebo + exercise versus AA + exercise
Fricker et al.[36]	29.5	Male and female	Trained shot-put, discus	Weightlifting circuit	1.8 g arg, 1.2 g orn, 0.48 g met, 0.12 g phe	Oral	Exercise ↑ GH; AA did not increase exercise-induced GH release
Fry et al.[37]	17.3 ± 0.3	Male	Elite junior weightlifters	7 d high-volume, weightlifting	2.1 g arg, orn, lys + 2.1 g BCAA + 50 mg gln	Oral	No difference placebo + exercise versus AA + exercise
Eto et al.[41]	18–22	Male	Highly trained cyclists	2-h cycling; 75–83% VO_{2max}	20 g arg glu	Oral	Exercise ↑ GH; AA ↓ exercise-related GH release
Wideman et al.[42]	25	Male and female	Recreationally active	30 min cycling; intensity > lactate threshold	30 g arg	IV	arg + exercise > placebo + exercise

* Data are presented as mean, mean ± standard deviation, or range.

AA, amino acids; arg, arginine; BCAA, branched-chain amino acids; GH, growth hormone; glu, glutamate; IV, intravenous; lys, lysine; met, methionine; orn, ornithine; phe, phenylalanine; RM, repetition maximum.

diets of 2.2 $g \cdot kg^{-1} \cdot d^{-1}$, which may mask or blunt a possible effect of amino acids on GH secretion.[15] Supplementation with an amino acid mixture consisting of 2.1 g of arginine, ornithine, and lysine, 2.1 g of BCAAs, and 50 mg of glutamine before each workout did not affect GH concentrations before or after 7 d of high-volume weightlifting in elite junior weight lifters.[37] Although BCAAs alone have minimal effect on GH levels,[5] consumption of BCAAs may reduce the GH response to exercise.[38] Ingestion of a mixture of BCAAs immediately before 1 h of running decreased GH levels postexercise compared with the placebo condition.[38] High serum BCAA levels may reduce synthesis of serotonin,[39] a potential stimulus for GH release,[40] in the brain. Interestingly, administration of 20 g of arginine and glutamate to highly trained cyclists before cycling at 75% to 83% of maximal aerobic power for 60 min greatly reduced the exercise-associated rise in plasma GH concentration.[41] The blunted GH response may be due to glutamate reducing the stimulatory effect of exercise on GH release.

Although no studies showed an enhanced exercise-induced GH release with amino acid consumption, infusion of 30 g of arginine coupled with 30 min of cycling exercise at an intensity greater than the power output required to achieve lactate threshold increased GH secretion compared with exercise alone in men and women.[42] This study is inconsistent with other studies showing that arginine or other amino acids do not augment exercise-induced GH release. This difference may be explained by the infusion of a high dose of arginine that may result in greater serum arginine levels compared with oral administration of lower doses. Oral consumption of amino acids at dosages large enough to effect a further increase in GH during exercise is likely to cause gastrointestinal discomfort and diarrhea,[12] which likely preclude routine use of these amino acids.

PHYSIOLOGIC SIGNIFICANCE OF EXERCISE-INDUCED INCREASES IN GH

The physiologic significance of the exercise-induced increase in GH is unclear. GH acts as an anabolic hormone via insulin-like growth factor-1 (IGF-1) to increase amino acid uptake and protein synthesis and as a metabolic hormone to stimulate lipolysis and reduce carbohydrate metabolism to maintain blood glucose levels.[43] Whether the exercise-induced GH response is significant with regard to its anabolic role is not known. Studies have reported increases in GH and IGF-1 after exercise.[44,45] However, other studies in which GH was elevated in response to exercise reported no change in IGF-1 levels[29,46] or changes in IGF-1 that were not correlated to changes in GH concentrations.[26,27] Also, circulating IGF-1 levels were not altered after oral administration of arginine and lysine.[14] Additional studies need to assess the GH and IGF-1 responses to amino acids and exercise.

GH treatment has a persistent lipolytic effect in GH-deficient individuals and obese subjects.[47,48] GH administration has a potent effect in increasing serum free fatty acid levels in normal-weight and obese subjects, consistent with its lipolytic action.[49,50] GH treatment increased fat loss in lean subjects[51] and obese subjects during caloric restriction.[48] However, GH treatment did not reduce body fat in male power athletes[52] or males of average body composition (16.6% body fat) in short-term studies.[53] The lipolytic effects of GH therapy may be related to the degree of adiposity and GH deficiency.[52] Although the significance of an increase in circulating GH levels during exercise or after amino acid consumption is unclear, GH may play a significant role in mobilizing free fatty acids for energy production.[43,49,50]

EFFECT OF AMINO ACIDS USED AS GH SECRETAGOGUES ON MUSCLE MASS AND STRENGTH

There is no evidence based on properly conducted, rigorous scientific studies that oral supplementation of specific amino acids induces GH release that, in conjunction with resistance training, increases muscle mass and strength to a greater extent than resistance training alone. Two studies that reported greater increases in body mass and reductions in percentage of body fat[54] and gains in total body strength and lean body mass[55] as a result of arginine and ornithine supplementation were seriously flawed by inappropriate statistical analyses.[56] In both studies, it appears that multiple dependent variables were included in a single analysis of variance and used as levels of an independent variable.[54,55]

Although specific amino acids such as arginine, lysine, and ornithine have not been shown to alter body composition in individuals engaged in strength-training programs, it may be of interest to the reader to point out that arginine and ornithine have been shown to reduce body weight loss and protein catabolism in experimental models and clinical situations.[57,58] These amino acids exert anticatabolic effects in part by stimulating GH secretion.[58] For example, enhanced wound healing in rats treated with dietary arginine depended on an intact hypothalamic–pituitary axis.[59] However, additional mechanisms may contribute to reducing body weight and protein loss in various clinical situations and experimental models.[57,58]

In addition, one must consider whether GH would enhance gains in muscle mass and strength in individuals engaged in strength-training programs. Although two studies reported that administration of GH to individuals undergoing strength training results in greater gains in fat-free weight than strength training alone,[60,61] experimental evidence suggested that the fat-free weight is non-contractile in nature.[53,61] Also, studies have not demonstrated greater gains in muscular strength with GH administration and strength training compared with strength training only.[52,60]

SUMMARY

The practice of consuming specific amino acids, in particular arginine, lysine, and ornithine, to increase GH levels during or after exercise does not appear to be effective. Infusion of specific amino acids[3–5] or consumption of large doses of specific amino acids can increase GH concentrations.[12] The GH response to amino acid consumption is highly variable[1] and reduced with aging[13] and in exercise-trained individuals.[12] The GH response also is lower in males than in females[3] and lower in individuals consuming diets high in protein.[11] Further, exercise is a potent stimulus for GH release, and oral supplementation of amino acids has not been shown to augment the exercise-induced GH increase.[7,36] The physiologic significance of the exercise-induced elevation in GH levels is not clear, and studies need to examine the effect of exercise and amino acid supplementation on IGF-1 levels. Moreover, there is no sound scientific evidence that supplementation with arginine, ornithine, or lysine is effective in altering body composition in athletes. The primary side effects of consumption of large quantities of amino acids are stomach cramping and diarrhea.[12] The use of specific amino acids for the purpose of stimulating GH release to promote greater gains in muscle mass and strength and to alter body composition is not recommended.

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(For an additional perspective, see Editorial Opinions)