Growth hormone, arginine and exercise

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Purpose of review

To describe the effect of an acute bout of exercise on growth hormone responses and to discuss the effect of L-arginine supplementation on growth hormone responses.

Recent findings

Recent studies have shown that resting growth hormone responses increase with oral ingestion of L-arginine and the dose range is 5–9 g of arginine. Within this range there is a dose-dependent increase and higher doses are not well tolerated. Most studies using oral arginine have shown that arginine alone increases the resting growth hormone levels at least 100%, while exercise can increase growth hormone levels by 300–500%. The combination of oral arginine plus exercise attenuates the growth hormone response, however, and only increases growth hormone levels by around 200% compared to resting levels.

Summary

Exercise is a very potent stimulator of growth hormone release and there is considerable research documenting the dramatic growth hormone rise. At rest oral L-arginine ingestion will enhance the growth hormone response and the combination of arginine plus exercise increases growth hormone, but this increase may be less than seen with exercise alone. This diminished response is seen in both in both younger and older individuals.

Keywords

exercise, L-arginine, somatotropin

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Introduction

At rest, the hypothalamus tightly controls growth hormone (GH) release by the anterior pituitary gland. GH-releasing hormone (GHRH) stimulates GH release and somatostatin inhibits it. GH release occurs in a pulsatile pattern [1,2], peaks at night and the peaks are in close association with slow wave sleep [2–4]. GH is part of the insulin-like growth factor (IGF) axis, thus as GH concentrations increase they stimulate the release of IGF-I. Elevated levels of GH cause autonegative feedback, resulting in a decline in GH secretion. There are numerous physiological stimulators of GH, but one of the most potent stimulators of GH is exercise; following exercise, it may take a few hours to recover back to baseline levels. Other factors that play a role in GH release at rest and during exercise are age, gender, body composition, nutrition, sleep, fitness level and sex steroid hormones [5]. It is speculated that the mechanisms responsible for exercise-induced GH release are the suppression of hypothalamic secretion of somatostatin and possibly during-high intensity exercise an augmented hypothalamic secretion of GHRH [6,7].

The primary function of GH release during exercise is not known. GH is known to be a metabolic hormone which stimulates lipolysis and reduces carbohydrate metabolism to maintain blood glucose levels. GH also causes the release of IGF-I, which increases amino acid uptake and protein synthesis [8]. Although GH is important in metabolism, it has a secondary role to catecholamines and insulin in regulating glucose and fat metabolism [9], and the exercise-induced increase in GH may be important for postexercise protein synthesis.

Exercise and growth hormone responses

Exercise of almost any type has been shown to elicit GH responses. The early studies in this area demonstrated that both continuous and intermittent exercise results in increased GH concentrations, and a significant increase does not appear until approximately 15 min into exercise [10,11]. Considerable controversy has existed about the optimal exercise intensity for GH release. Early work [12] noted that short-duration (10 min), low-intensity exercise did not cause a GH response, but that short-duration, high-intensity exercise increased GH levels significantly.

Likewise, Sauro and Kanaley *et al.* [11] also demonstrated that short-duration, moderate-intensity exercise (75% VO_2 max, for 10 min) is adequate to cause an exercise-induced GH response. As seen in studies employing longer exercise durations, the GH increase can be as much as 300–500% above resting values, with values ranging from 15 to 20 μg/l [13], and this increase can be sustained for as long as 3 h post-exercise [10]. There is a linear dose–response pattern of GH secretion with increasing exercise intensities [14]. Low intensities of aerobic exercise stimulated GH responses and with each increment in exercise intensity the fractional increase in GH secretion was greater in women than in men [15]. Although resistance exercise and GH release has not been as well studied, there is considerable evidence showing that high-intensity resistance exercise will increase GH levels, but that the rest periods need to be less than 90 s [16].

The magnitude of the exercise-induced GH response is independent of the time of day [10,17], indicating that aerobic exercise appears to override the diurnal rhythm underlying the GH release. Since the hypothalamus is controlled by negative feedback the impact of multiple bouts of exercise on the GH response has been questioned. Integrated GH concentrations increased with subsequent exercise bouts, whether the bouts were spaced 1.5 or 4 h apart. Slightly greater increases in integrated GH concentrations were seen when the bouts were 4 h apart than when they were 1.5 h apart [18]. This implies that exercise is a powerful stimulus of GH release that is able to override GH autonegative feedback. It also suggests that the pituitary is capable of producing and storing large quantities of GH [18]. Further, this daytime increase in GH does not change nocturnal GH release [18,19].

The effects of exercise training on GH secretion have been controversial. The exercise-induced GH response has been shown to decrease with a short-duration (6 weeks), high-intensity training program when the same absolute workload was performed post-training [20]. This suggested that the GH response to exercise is determined by the relative workload rather than the absolute workload. A 1-year training program augmented the pulsatile release of GH when training was above the lactate threshold [20], but not when it was below the lactate threshold. Although there are few studies reporting on exercise training in elite athletes or on overtraining, there is research showing that amenorrheic athletes have a greater number of pulses, a decease in half-life of GH and a decrease in the mass of GH secreted per pulse when compared to eumenorrheic women during 8 h of nocturnal blood sampling [21], which suggests that exercise alters the GH–IGF axis.

Clinical implications of growth hormone for aging, increasing muscle mass and growth hormone use in athletes

The importance of adequate GH levels and the impact on exercise performance and body composition has only been appreciated during the past two decades. GH-deficient adults, whether caused by hypothalamic or pituitary disease, have alterations in body composition, with marked reductions in lean body mass and excess body fat when compared with individuals with adequate GH levels [22]. Research has shown that GH administration to GH-deficient children or adults results in gains in lean body mass and muscle strength within months of treatment being initiated [23–26]. Additionally, much of the research in the late 1980s and 1990s has touted GH to be an antiaging drug [27], with the link between exercise and longevity being the increased release of endogenous GH stimulated by exercise [28]. A recent review of randomized, controlled trials evaluating GH therapy in older individuals, however, suggests that only small changes in body composition (change in fat mass: −2.1 kg; change lean body mass: 2.1 kg) are observed and there are increased rates of adverse events [29••]. These authors concluded that GH is not recommended for antiaging therapy. Furthermore, the research does not conclusively demonstrate a strong link between GH administration and increased muscle mass, strength or performance in a younger population. No changes in body composition or protein synthesis were found following treatment with GH in double-blind, placebo-controlled studies [30–32]. In studies where increases in strength were observed, the improvements occurred in both the exercise and GH-supplemented groups. Regardless of the research findings, athletes are aware of the potential benefits of GH administration and the potential effects on performance. The suspected use of GH in athletics has risen in the past decade and GH is currently the ideal drug because of the lack of reliable testing to identify users [28]. To date, there is no research that demonstrates a significant increase in work capacity in response to human GH administration in healthy adults [28].

Arginine and growth hormone response

Resting GH secretion can be increased dramatically by an intravenous administration of various amino acids including: arginine, methionine, phenylalanine, lysine and histidine [8,33]. Leucine and valine are less potent in stimulating GH, and isoleucine does not affect plasma GH concentrations [8]. In the late 1960s, Merimee *et al.* [34] recognized that an intravenous infusion of arginine as well as other amino acids dramatically stimulated GH release in both men and women. Intravenous arginine

infusion has been used clinically to determine the responsiveness of the GH axis when GH deficiency is suspected. Research has also been conducted demonstrating that oral ingestion of arginine also increases GH levels at rest [35]. Plasma concentrations of GH increase 2 to 4.5-fold higher in comparison with controls following oral ingestion of glutamine or arginine [35,36] or a combination of arginine and lysine [37,38].

Although previous work had been done examining the effects of arginine ingestion on GH levels, establishing the correct dose of arginine is critical. Much of the early work used intravenous GH and these studies used very high doses of arginine (2–40 g). Collier *et al.* [35] attempted to establish the ideal dose for ingestion of oral arginine. On four separate occasions, subjects received placebo, 5, 9 or 13 g of L-arginine (randomized and blinded) and blood samples (every 10 min) were drawn for the following 5 h. An increase in the peak GH and area under the curve response was seen with increasing doses of arginine up to 9 g. Both peak levels as well as area under the curve were greatest with the 9 g of arginine and the time course demonstrated that peak levels were 30 min post-ingestion.

Arginine, growth hormone and exercise

Both exercise and arginine are known to be clear stimulators of GH release independently in most individuals, and there has been considerable research about the combined effect on the GH response. In a recent study, Collier *et al.* [39••] examined the combined effect of arginine (7 g) and resistance exercise on the GH response in healthy young males. Arginine alone resulted in a significant GH response (2-fold increase) over the placebo day, while exercise alone stimulated a 5-fold increase. An attenuated GH response was observed when arginine plus exercise were combined, demonstrating a three-fold increase. Interestingly this study demonstrated that an adequate dose of oral arginine can stimulate an almost 200% increase in GH levels when combined with exercise, but this was still around 50% less than observed on the exercise-alone day.

These findings are closely aligned with earlier studies using oral arginine either alone or in combination with other amino acids. Suminski *et al.* [38] had subjects ingest a combination of L-arginine and L-lysine (1500 mg each), and followed this with resistance exercise. Exercise resulted in increased GH levels, yet the amino acid ingestion resulted in no differences in the GH response. Thus, this amino acid combination did not alter the exercise-induced GH changes in young men, but at rest when the amino acid combination was ingested there was a significant GH response. Marcell *et al.* [40] also conducted a similar study but examined the arginine (5 g) plus exercise responses in young and older individuals. The administration of oral arginine did not significantly change basal GH concentrations in either young or old individuals nor did it enhance the GH response to exercise in either group. The GH response was increased with arginine alone, but a greater increase was found with exercise alone in the young subjects. There was a tendency for a blunted GH response when arginine was combined with exercise; however, this blunting was not observed in older subjects who had a much smaller GH response initially [40]. This finding was similar to that reported by Collier *et al.* [39••].

Studies have also examined the effect of short-term supplementation on the GH responses. Using a double-blind crossover protocol, Fogelhom *et al.* [41] studied the effects of a 4-day combined L-arginine, L-ornithine and L-lysine supplementation (2 g/day in two doses) on 24-h GH levels in weight lifters. Supplementation did not affect the physiological variation of serum GH or insulin concentrations. The ergogenic value of low-dose oral arginine ingestion for amino acid supplementation is questionable in healthy young individuals. Likewise, Abel *et al.* [42] questioned whether arginine effects would be apparent in healthy individuals. They investigated whether the daily intake of two different doses of arginine aspartate for 4 weeks affected parameters of overtraining syndrome in 30 male endurance trained athletes. These athletes either ingested arginine aspartate in a high dose (5.7 g arginine/8.7 g aspartate) or low dose (2.8 g arginine/2.2 g aspartate), or a placebo. Compared to placebo, no differences in maximal oxygen consumption, time to exhaustion, GH, glucagon, cortisol or testosterone concentrations were observed, and there was no difference between groups for dosage. Again this infers that arginine supplementation is not an effective ergogenic aid in healthy individuals.

The mechanism for the increase in GH with arginine is suspected to be by inhibition of endogenous somatostatin release [43]. Although the mechanism has not been specifically outlined, it is speculated that if arginine induces GH release via somatostatin and if the exercise-induced GH release is preferentially mediated by somatostatin withdrawal then potentially these two methods should be additive. Oral arginine taken about 30 min prior to exercise may cause an autonegative feedback on the somatotrope; thus it does not respond as efficiently as it would to just the exercise alone. The somatotrope is also known to have a refractory period when subjected to repeated GHRH stimulation due the autonegative feedback [44–47] and possibly the 30-min time period falls within that refractory period, and this becomes an issue of appropriate timing between the arginine ingestion and the exercise.

In contrast to the above findings, however, there is one study that coupled intravenous arginine with aerobic, constant load exercise. In this study, 30 g of intravenous arginine was administered immediately prior to exercise. GH area under the curve was slightly larger with arginine plus exercise than exercise alone and Wideman *et al.* [48] reported a doubling of GH secretory burst mass by arginine plus exercise vs. exercise alone. They concluded that exercise releases both GHRH and somatostatin, and L-arginine may limit somatostatin release. The dose of the arginine infusion used in the Wideman study (30 g of intravenous arginine) may, however, have overwhelmed the system, resulting in the higher GH response with arginine plus exercise than exercise alone. Studies using smaller doses (1500 mg to 9 g) taken orally 30 min prior to exercise may be reflecting the autonegative feedback from the arginine ingestion.

Conclusion

In GH-deficient children/adults, GH administration results in increased muscle mass and decreased body fat, and based on this information many athletes have started to use GH. The current evidence does not support the increase in muscle mass with arginine supplementation (subcutaneous or oral administration) and there are side effects (e.g. soft tissue edema, carpal tunnel syndrome, arthralgias and gynecomastia [29••]) associated with its use. Lastly, acute use of oral arginine (around 30 min prior to exercise) seems to blunt the GH response to subsequent exercise and may have negative metabolic consequences, which has not been studied to date, relative to exercise alone.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 82).

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