Effects of an Amino Acid-Based hGH Secretagogue on Triiodothyronine

ABSTRACT

Background: In a recent randomized, double-blind, cross-over clinical trial, serum growth hormone (hGH) increased 8-fold above baseline 120 minutes after oral administration of an amino acid-based dietary supplement (Protovale™), p=0.01 vs. placebo. In contrast to the mechanism of hGH stimulation by ghrelin, we hypothesize that the supplement suppresses somatostatin, a known inhibitor of both hGH and TSH. To test this hypothesis, we measured triiodothyronine (T3) after administration of the amino acid-based supplement.

Methods: Sixteen healthy subjects [12 males, 4 females; mean age= 32±14 years; BMI=26.4±5.0 kg/m2] participated in a double-blind, placebo-controlled, cross-over trial. After an overnight fast, T3 concentrations were measured at baseline and 120 minutes after consuming the placebo or the amino acid-based supplement. Differences were compared to baseline by independent t-tests and to each other by paired t-tests. Statistical significance was set at p<0.05.

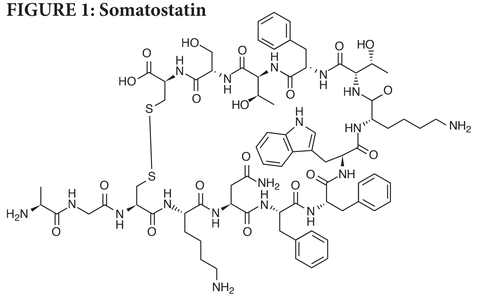
Results: After placebo administration, T3 concentrations significantly dropped by 6.1±8.5ng/dL (mean±SD) (106ng/dL at time 0 to 100ng/dL at 120 minutes, p=0.01). This decrease was expected due to the normal circadian drop of T3 during the morning hours. However, after administration of the amino acid supplement, the magnitude of the T3 drop was blunted by nearly 50%, 3.3±10.3ng/dL (101ng/dL at time 0 to 97.6ng/dL at 120 minutes, NS), whereas the final T3 concentration was not significantly reduced from baseline. There was no difference in the T3 reduction between the supplement and placebo conditions, 2.8±11.8ng/dL (p=NS).

Conclusion: Maintenance of triiodothyronine levels by the amino acid-based supplement but not by the placebo adds support to the hypothesis that somatostatin inhibition may be responsible for the observed increase in hGH by Protovale™ in healthy men and women. This mechanism is in contrast to ghrelin mimetics for increasing hGH, which are associated with increased hunger. The direct support of T3 may provide additional metabolic advantages, an outcome to be investigated in subsequent studies.

INTRODUCTION

Two molecular targets that regulate the synthesis and secretion of human growth hormone (hGH) include 1) ghrelin, an endogenous ligand secreted by the stomach that also has appetite-stimulating properties distinct from its hGH-stimulating effects, and 2) somatostatin, a family of 14 and 28 amino acid peptides that act as a potent noncompetitive inhibitor of the release of hGH. (1,2) We recently reported that oral administration of a 2.9g/dose of Protovale™, a blend of l-lysine HCl, l-arginine HCL, oxo-proline, N-acetyl-l-cysteine, l-glutamine, and schizonepeta (aerial parts) powder, leads to a significant 8-fold mean increase in endogenous hGH levels in male and female subjects in a period of 120 minutes following acute consumption. In the work presented here, we seek to characterize the mechanistic target associated with this measured increase in endogenous hGH by Protovale,™ which we hypothesize to be somatostatin, Figure 1. We test this hypothesis by assaying thyroid function, a secondary inhibition target of somatostatin. We further compare our findings to ghrelin-based hGH secretagogues.

FIGURE 1: Somatostatin



METHODS

The acquisition of the experimental blood serum samples analyzed here has been described previously.(3) Briefly, the trial was conducted with a cross-over, placebo controlled, double-blind design with a one-week washout period. On test days, the 16 healthy subjects [12 males, 4 females; mean age= 32±14 years; body mass index=26.4±5.0 kg/m2] arrived at the facility after an overnight fast and had an IV line placed and blood samples drawn at baseline and incrementally over 120 minutes after consumption of Protovale™ or placebo. In this investigation, the baseline and 120 minute blood samples were assayed for total triiodothyronine (T3), as T3 is physiologically activated by thyroid stimulating hormone (TSH), a direct inhibition target of somatostatin. T3 is an ideal assay parameter because it has a longer half-life than TSH (2.5 days vs. 1 hour for T3 and TSH, respectively), making it conducive to accurate measurement. Total circulating T3 in the serum was measured on the Siemens Medical Solutions Diagnostics Immulite 2000.

STATISTICAL METHODS

Differences were compared to baseline by independent t-tests and to each other by paired t-tests. Statistical significance was set at p<0.05.

RESULTS

Mean T3 levels at baseline for the Protovale™ and placebo groups were measured at 100.9±19.4 and 106.2±17.0ng/dL, respectively. At the 120 minute time point, the Protovale™ group changed only marginally with a mean T3 of 97.6±18.4ng/dL, p=NS vs. baseline, whereas the T3 levels for the placebo group significantly decreased to 100.1±15.9ng/dL, p=0.01 vs. baseline), Table 1. There was no significant difference between groups, 2.8±11.8ng/dL (p=NS).

As daily circadian levels of T3 naturally decrease during the morning hours at which the current trial was scheduled, *(4)* it was expected that placebo levels over the 120 minute time frame would decrease significantly as measured, -6.1±8.5ng/dL (106 to 100 ng/dL, P=0.01). In contrast, the blunting of T3 decrease in the Protovale™ group by nearly one-half over the same time course, -3.3±10.3ng/dL (101 to 97.6 ng/dL, NS), supports the hypothesis that somatostatin inhibition plays a mechanistic role in the ability of Protovale™ to induce significant increases in serum hGH levels in human subjects.

TABLE 1:

	Baseline (ng/dL)	120 Min (ng/dL)	GGG (ng/dL)	p[i]
Protovale™	100.9±19.4[ii]	97.6±18.4	-3.3±10.3	NS
Placebo	106.2±17.0	100.1±15.9	-6.1±8.5	=0.01

[i] *compared to baseline by independent t-tests*
[ii] *mean±SD*

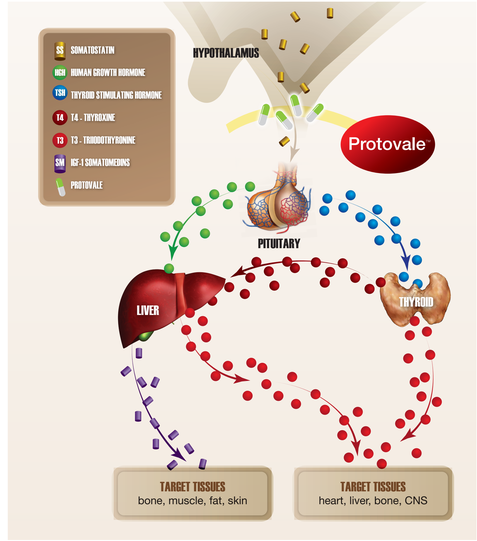
DISCUSSION

Oral hGH secretagogues generally fall into one of two mechanistic categories, acting either by ghrelin pathway stimulation or somatostatin inhibition. Ghrelin and its mimetics act as an endogenous ligand for growth hormone secretagogue receptor (GHSR), wherein its binding to GHSR leads to hGH secretion. Importantly, ghrelin also has appetite-increasing activities distinct from its hGH-stimulating effects and often causes subjects to gain weight and even body fat. *(2,5-7)* While such gains may be useful in cases of sarcopenia, *(8,9)* a condition of loss of muscle mass and wasting, this is not typically a desired outcome in healthy aging. In contrast, somatostatin inhibition leads to increased serum hGH as well as serum TSH, with a downstream supportive effect on T3, as shown in Figure 2, which is consistent with our Protovale™ results. The advantages of the somatostatin inhibition mechanism include the absence of the hunger-inducing effects of ghrelin as well as potential additional metabolic advantages separate from those of hGH through the direct support of thyroid function.

CONCLUSIONS

In conclusion, our results showing that Protovale™ blunts the drop in morning T3 levels by nearly 50% compared to placebo supports the hypothesis that somatostatin inhibition is the mechanistic target by which Protovale™ increases serum hGH levels by a mean of 8-fold, equivalent to 682%, in healthy men and women of a relatively wide age range. The advantages of somatostatin inhibition as compared to ghrelin pathway stimulation is the absence of the hunger-inducing effects of ghrelin as well as potential metabolic advantages through direct thyroid support.

FIGURE 2: Hypothalamic–Pituitary–Thyroid (HPT) axis



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