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Chapter 16

Secretagogues: An Alternative to Recombinant Human Growth Hormone

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ABSTRACT

Objective: To examine the efficacy of a compound of mixed amino acids, GABA, and *Mucuna pruriens* enveloped in a nanoliposomal delivery system to increase the production of growth hormone (GH), insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding protein 3 (IGFBP-3), in healthy individuals.

Design and Method: Within a private medical office, healthy individuals were screened for GH insufficiency (150-101 ng/ml IGF-1) and deficiency (less than 100 ng/ml IGF-1) prior to being given the secretagogue (Secretropin®). A morning dose of the preparation, 0.20 cc (600 mg) was placed under the tongue for 30 seconds prior to swallowing. A bedtime dose of 0.40 cc (1200 mg) was placed under the tongue for 30 seconds prior to swallowing. At both times the participant refrained from eating or drinking for at least 30 minutes prior to and after taking the secretagogue. Laboratory testing of at least IGF-1 and IGFBP-3 was performed prior to starting the secretagogue and at 1, 3, and 6 months.

Results: After a twelve-month testing period, the secretagogue was shown to increase patients' circulating levels of IGF-1 by 50-200% in 92% of the participants.

Conclusion: This nanoliposome delivered secretagogue was shown to be capable of elevating natural GH production and release in healthy individuals, as evident by elevated levels of IGF-1 and IGFBP-3.

INTRODUCTION

The recognition and acceptance of non-peptide, synthetic complexes as potent growth hormone (GH) secretagogues has been less than positive due to a number of perceived limitations.

These perceptions were based upon our lack of scientific evidence to support the supposition that something other than a complex peptide, such as growth hormone releasing hormone (GHRH) could increase a hormone's production.[1] Additionally, we lacked the scientific knowledge about flexible receptors that could accept a broad range of chemical structures that would lead to the stimulated production or suppression of a hormone.[2] Finally, we are starting to understand more about the complex influences that hormones, peptides, and amino acids have on the hypothalamic-pituitary axis.[3,4]

Firstly, past research data was based upon small test groups of individuals that were given large quantities of mixed amino acids designed to enhance GH production and release. Although many of these compounds demonstrated a measurable elevation in the GH/ insulin-like growth factor 1 (IGF-1) axis, many were also associated with osmotic diarrhea, making it a difficult pill to swallow.[5,6] Secondly, delivery of amino acids by mouth has a poor bioavailability due to its destruction and inactivation by gastric acid. A large compensatory dose is then needed to correct for this diminished availability thereby, leading to the side-effect of diarrhea. Thirdly, since the action of a secretagogue is to increase the amplitude and duration of intrinsic GH secretion, the normal regulatory or homeostatic mechanism (positive feedback and negative feedback) is preserved. When a secretagogue elevates the intrinsic production of GH above the body's inherent set-point, Somatostatin release (also known as somatotrope release inhibiting factor (SRIF)) causes the suppression of intrinsic GH production. This, in turn, can lead to the waxing and waning of GH/IGF-1 levels, making it difficult to accurately assess the net affect.

These issues have generated the majority of resistance to the use of secretagogues in healthy individuals with low GH, IGF-1, and insulin-like growth factor binding protein 3 (IGFBP-3) levels.

This paper will present current, evidence-based scientific literature, and clinical results to support the use of a secretagogue as a responsible "first step" approach to the treatment of GH deficiency in healthy individuals.

HISTORY

Amino Acids as Growth Hormone Secretagogues

Ornithine

Ornithine is derived from the amino acid arginine. High doses of oral ornithine have successfully raised GH levels. Bucci *et al* investigated the effect of 40, 100 and 170 mg/kg of oral L-ornithine HCl. 25% of the subjects experienced a significant increase in their serum GH level at the two lower doses, while 50% of the subjects showed an increase in GH at the highest dose. GH levels increased up to four times higher than the baseline level.[7]

Arginine

Arginine (Arg), when taken in large quantities, has also been noted to increase the serum levels of GH, IGF-1 and IGFBP-3.[8] The mechanism of this stimulated increase has since been found to be due to the suppression of somatostatin release.[9,10]

Ornithine-alpha-ketoglutarate (OKG)

Ornithine alpha-ketoglutarate (OKG) is formed of two molecules of ornithine and one molecule of alpha-ketoglutarate. OKG is a promising anti-catabolic agent that promotes wound healing and protein synthesis. Researchers have hypothesized that OKG fulfills these functions by encouraging the secretion of insulin and GH, and by upregulating glutamine and arginine production. When fed enterally to trauma patients, OKG significantly increased both IGF-1 and GH levels.[11]

Arginine and Lysine

During resting conditions, GH was significantly elevated 60 minutes after consumption of arginine and lysine compared with the placebo trial. The researchers concluded that ingestion of 1500 mg arginine and 1500 mg lysine before resistance exercise did not alter exercise-induced changes in GH in young men. However, when the same amino acid mixture was ingested under resting conditions, an acute increase in GH secretion occurred.[12]

Glycine

Glycine is a non-essential amino acid contained in gelatin protein and is an important component of collagen. Although early research focused on glycine's ability to increase strength in athletes, more recent research has shown the reason this occurred was the result of its GH-boosting capabilities (with females experiencing a 22% increase and men a 32% increase in cycle ergometry workloads after ingestion of 5-12 g of glycine daily).[13,14]

One study clearly illustrated glycine's ability to act as a GH secretagogue. When 19 normal, non-obese subjects consumed 6.75 g of glycine orally, GH levels significantly increased for 3 hours, reaching a maximum of 3 to 4 times that of baseline at 2 hours. According to the researchers, glycine is one of the stimulatory agents inducing the pituitary gland to secrete GH.[14]

Glutamine

Glutamine is the most abundant amino acid in human muscle and plasma, directly regulating both the production and wearing-down of protein, as well as immune cell activity.[15] When healthy subjects consumed 2 g of oral glutamine 45 minutes after a light breakfast, 89% of the subjects experienced elevated plasma GH within 90 minutes. These findings demonstrate that a small oral glutamine load is capable of elevating plasma GH. Glutamine is converted into citrulline in the small intestine, which in turn triggers the synthesis of arginine, an amino acid shown to increase the release of GH by suppressing somatostatin release.[9,10] Moreover, glutamine is converted into glutamate, which directly enhances GH secretion.[16-19]

GABA

Gamma-aminobutyric acid (GABA) is the brain's major inhibitory neurotransmitter. Studies have shown that GABA is responsible for both the rise of GH (when at rest) and the inhibition of GH (when exercising). Oral GABA supplementation has increased GH levels in humans. In one study, a single oral dose of 5 g of GABA administered to 19 subjects significantly elevated plasma GH levels compared to

placebo-treated controls.[20] A number of studies have demonstrated that alcohol consumption abolishes the ability of GABA to affect the secretion of GH.[21]

Mucuna Pruriens

Also known as the velvet bean, *Mucuna* contains a significant amount of extractable L-dopa (L-3,4-dihydroxyphenylalanine) in its seeds and roots.[22] Unique to this natural form of L-dopa is its rapid absorption and bio-availability, and low potential for toxicity when compared to the pharmaceutical, synthetic product.[23,24]

When L-dopa/dopamine binds to the DR2 cell receptors in the brain, an atypical neuroregulatory mechanism leads to the stimulation of GH production and release.[25, 26] The elucidation of this relationship has been tested in obese premenopausal women who have suppression of dopamine production by virtue of their obesity. Bromocriptine use improved upon the circadian GH secretion which added support to the role of Dopamine Receptor-2 as an adjunctive means of stimulation of GH secretion.[27]

Liposomal Delivery Technology

A liposome is a spherical vesicle composed of a bilayer membrane. In biology, this refers to a membrane composed of phospholipids, and a cholesterol bilayer. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chains (like egg phosphatidylethanolamine), or of pure surfactant components like DOPE (dioleoylphosphatidylethanolamine). Liposomes, usually but not by definition, contain a core of aqueous solution; lipid spheres that contain no aqueous material are called micelles, however, reverse micelles can be made to encompass an aqueous environment.[28]

Liposomes were first described by British hematologist Dr Alec D Bangham FRS in 1961, at the Babraham institute, Cambridge. They were discovered when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. The resemblance to the plasmalemma was obvious, and the microscopic pictures served as the first real evidence for the cell membrane being a bilayer lipid structure.[29]

Liposomes are used as drug delivery systems due to their unique properties. A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane, preventing dissolved hydrophilic solutes from readily passing through the lipids. Hydrophobic chemicals can be dissolved into the membrane, and in this way the liposome can carry both hydrophobic molecules and hydrophilic molecules. To deliver the molecules to sites of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents. By making liposomes in a solution of DNA or medication (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer.[29]

Liposomes can also be designed to deliver drugs in other ways. Liposomes that contain low (or high) pH can be constructed such that dissolved aqueous drugs will be charged in solution (i.e., the pH is outside the drug's pH range). As the pH naturally neutralizes within the liposome (protons can pass through some membranes), the drug will also be neutralized, allowing it to freely pass through a membrane. These liposomes work to deliver the drug by diffusion rather than by direct cell fusion. Another strategy for liposome drug delivery is to target endocytosis events. Liposomes can be made in a particular size range that makes them viable targets for natural macrophage phagocytosis. These liposomes may be digested while in the macrophage's phagosome, thus releasing its drug. Liposomes can also be decorated with opsonins and ligands to activate endocytosis in other cell types.[30]

RESEARCH DESIGN

The goal for the study was to enroll 50 healthy male and female participants. Enrollment into the study was open with the only restriction being no active use of psychotropic medication or recombinant human growth hormone (rhGH). Each participant had a comprehensive chemical and hormonal panel drawn prior to starting the secretagogue. Instructions for the use of the secretagogue were standardized to 600 mg in the morning (by oral delivery) and 1200 mg at bed time (by oral delivery). Each participant was instructed to avoid eating and drinking for 30 minutes prior and after delivery of the product. Two pumps (0.2 cc) of the spray were delivered under the tongue and held for 30 second in the morning and 4 pumps (0.4 cc) at bed time. With each dosing the participant was instructed to hold the fluid under their tongue for 30 seconds and then swallow.

Participants were acting as self controls, since their baseline hormone levels were obtained prior to initiation of secretagogue treatment and therefore, upon stopping, the anticipated drop-off in IGF-1 and IGFBP-3 would be used to indicate withdrawal of the products effects.

An attempt was made to standardize patient laboratory testing (Table 1) at 0, 1, 3, 6, and 12 months. Laboratory testing included at minimum serial IGF-1 and IGFBP-3 levels. Additional testing was patient-specific as indicated in Table 1.

A response to the secretagogue was identified based upon elevation of IGF-1 and/or IGFBP-3. Important to the efficacy of the secretagogue is that all underlying hormone insufficiencies are corrected to levels of a 25-35 year old.

Table 1. Laboratory Testing

Initial	Subsequent	Abbreviation	Hormones
√	√	IGF-1	Insulin-Like Growth Factor-1
√	√	IGFBP-3	Insulin-Like Growth Factor Binding Protein - 3
√	√	F(T)	Free Testosterone
√	√	DHT	Dihydrotestosterone
√	√	DHEA-s	Dehydroepiandrosterone
√		E1	Estrone
√	√	E2	Estradiol
√		TSH	Thyroid Stimulating Hormone
√		FT4	Free T-4 (Tetraiodothyronine)
√		FT3	Free T-3 (Triiodothyronine)

RESULTS

The following data in Table 2 represent 49 participants who completed at least 6 months of active secretagogue use with clinical follow-up.

Table 2. Study Results

	Age	BMI	Initial IGF-1	Initial BP-3	1st Post IGF-1	1st Post BP-3	2nd Post IGF-1	2nd Post BP-3	3rd Post IGF-1	3rd Post BP-3
1	33	23.0	149.0	4393	187.9	4623	227.4	4485		
2	37	27.6	107.0	4197	140.0	4140	237.7	4653		
3	48	31.3	115.0	2674	167.0	3872	211.0	4319		
4	45	29.9	122.0	5450	290.0	6527	276.2	6233	246.9	5693
5	63	28.7	77.0	4490	123.0	4659	187.0	4709		
6	57	20.0	92.0	4090	219.0	4485	232.1	4573		
7	54	24.9	114.0	4280	197.7	4917	220.8	5290	119.2	4083
8	50	26.7	190.0	4485	233.8	4572				
9	56	32.2	58.0	2743	104.0	2984	122.3	3738		
10	40	30.3	99.0	2487	196.9	4227	207.6	4312		
11	37	37.0	199.2	5175	197.7	4543				
12	39	26.3	123.0	3791	176.2	4169	202.3	4427		
13	55	29.8	156.9	4370	123.8	4284	110.8	3630	89.2	3776
14	62	30.7	116.0	3120	149.0	3750	196.3	3827		
15	48	27.9	145.5	7361	227.4	6943				

Table continues on next page

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16	47	26.1	122.0	5520	236.9	5233	220.0	5463		
17	28	23.6	154.0	2830	240.0	3882	290.8	3767	309.6	4200
18	40	22.2	223.0	4993	265.0	5376	247.7	5607		
19	53	25.4	171.0	4850	286.9	4600	262.3	5377		
20	50	20.7	99.0	4130	213.0	5147	267.0	5262		
21	54	24.0	118.0	4210	213.8	4370	234.3	4193		
22	42	30.1	163.1	4313	253.7	4528				
23	30	34.7	217.0	4138	256.0	4322				
24	52	31.3	91.0	3824	150.8	5237	177.4	5514		
25	59	32.1	154.0	3139	136.0	4664	167.0	4832		
26	53	25.8	109.0	5430	167.7	4514	213.5	4768		
27	71	23.8	145.0	4785	166.0	4140	223.0	4385		
28	50	34.1	156.2	4629	197.0	4893				
29	44	21.4	177.0	4330	225.0	5031	205.4	4715	138.0	3500
30	47	25.5	116.0	3156	287.0	5704				
31	69	28.8	121.0	3241	125.0	3720	125.4	3278		
32	51	22.4	163.8	5549	206.2	4428	213.1	4227		
33	58	24.9	135.0	3659	177.0	4387	236.0	4427		
34	43	28.9	147.0	4950	226.4	5567				
35	43	30.6	172.0	4420	247.3	4732				
36	47	28.1	113.1	3623	162.0	3900	158.0	4400	Gene	Arnold
37	59	22.6	123.8	2579	146.2	2510	169.0	3110	150	2900
38	38	25.7	115.0	NA	193.1	4830	216.2	3680	295.4	4658
39	38	27.0	140.0	4200	237.7	4140				
40	41	30.1	88.5	2361	119.2	1949	103.0	2290	103	2300
41	53	26.1	236.0	4500	284.0	5400	233.0	5400		
42	57	33.0	65.0	NA	58.0	NA	104.0	NA	122.3	3738
43	40	26.3	123.0	NA	176.2	4169	182.3	5693	140.8	3249
44	38	26.1	166.0	NA	236.9	5233	281.0	5200		
45	33	27.7	137.7	5779	213.8	3968	230.0	4687		
46	54	26.1	191.0	4850	286.9	4600	262.3	5377	153.8	3824
47	54	28.2	91.0	NA	150.8	3824	120.0	3680	116.9	4428
48	43	24.7	163.1	4313	280.8	3882	143.8	4313		
49	50	33.2	145.4	7361	182.3	8453				
50										

DISCUSSION

A review of the above results shows a wide range of patient-specific improvement in IGF-1 and IGFBP-3 levels. As opposed to a comparative analysis of these results, we chose to use patient-specific improvement as a marker for response to the secretagogue. The concept of patient-specific improvement deals with the evaluation of an individual's unique response to the secretagogue over their baseline IGF-1 and IGFBP-3 levels, and not across the spectrum of all patients in the study. For example, patient #34 had an initial IGF-1 of 147 ng/ml and a subsequent level of 226 ng/ml at 3 months, representing a 54%

increase. Patient #17 had an initial IGF-1 of 154 ng/ml and a subsequent level of 309.6 ng/ml at 3 months, representing a 101% increase. Finally, patient #20 had an initial IGF-1 of 99 ng/ml and a subsequent level of 267 ng/ml at 3 months, representing a 169% increase. Subjective improvement correlated best with the percentage increase rather than the actual numerical increase in IGF-1 levels.

The need to measure IGFBP-3 (BP-3) is based upon research that shows approximately 95% of the IGF-I is bound to BP-3, which makes this protein the major carrier of IGFs in plasma. A principal function of BP-3 is to extend the half-life of the IGFs from 8 minutes to hours. The serum level of BP-3 appears to be constant over 24 hours and the protein was found to be GH dependent, which makes the detection of BP-3 very useful in the evaluation of GH secretion as generated by a secretagogue. A single BP-3 measurement correlates significantly with the logarithm of spontaneous GH secretion. In this study, there were noted participants who achieved a measurable elevation in BP-3 while the change in the level of IGF-1 was negligible.

GH production is regulated through circadian homeostasis. Any increase above the physiological level induces Somatostatin release from the hypothalamic supra optic nuclei precipitating feedback inhibition. Somatostatin works through three central mechanisms: (1) inhibition of GHRH production from the hypothalamic periventricular nuclei; (2) down-regulation of GHRH receptors; and (3) direct inhibition of pituitary somatotroph substrate-receptor interaction. Therefore, it is not unexpected to find patients with subsequent levels of GH markers lower than pre-treatment levels after use of a secretagogue. What has happened on a physiologic basis is that the level of GH exceeded the natural set point for that individual, causing inhibition of further GH production.

At this point in the ongoing study of this secretagogue, there was an 8% failure to respond in the study population. This may be explained by issues of patient compliance, secondary hormonal deficiencies, abnormal gastric absorption, or adverse interactions from other medications.

The key issue relative to patient compliance was the lack of proper application, dosing, and timing of administration of the secretagogue.

With regard to secondary hormonal deficiencies, the literature clearly cites a diminished responsiveness to GHRH when there is a concurrent deficiency of DHEA, testosterone, estrogen, DHT, dopamine, melatonin, and thyroid hormones. Therefore, if a secretagogue is used to upregulate the production of GH, any deficiencies of the aforementioned hormones would lead to a less than optimal production of GH.[32,33]

Abnormal gastric absorption refers to conditions such as food allergies, inflammatory bowel disease, ulcers, and underlying bacterial infections (*Helicobacter pylori*) that may have influenced the absorption of the secretagogue by the gastrointestinal tract.

Finally, there are a number of medications which are known to affect GH regulation which may have influenced the effectiveness of the secretagogue (see Table 3).

CONCLUDING REMARKS

In life, GH homeostasis is influenced by a number of internal and external factors (Table 3), many of which are coupled together in a synergistic relationship to maximize the efficiency of the body to produce more. It would seem from the vast number of articles reviewed, that the production and preservation of both GH and IGF-1 is of paramount importance to the persistent function of our body. The fact that GH has a 20 minute half-life, IGF-1 an 8 minute half-life, IGF-1 bound to IGFBP-3 a 20 hour half-life (± 4hours), and IGF-1/IGFBP-3 bound to Acid Labile Subunit (ALS) a 200+ hour half-life, indicates that the continued presence of IGF-1 is important to our survival.

The ability of a secretagogue to elevate production and release of GH is a complex process predicated by the net affect of factors that stimulate and those that suppress. The markers for identifying this net affect are based upon changes seen in both IGF-1 and IGFBP-3 levels. In this study using a secretagogue, the changes seen in IGF-1 and BP-3 levels were comparable to those levels seen in patients using rhGH.

Therefore, it would stand to reason that the responsible first step to GH replacement therapy is the administration of a GH secretagogue.

Table 3. Regulation of GH Production

Stimulation	Inhibition
GHRH	Somatostatin (SRIF)
Hypoglycemia	Hyperglycemia
Decreased free fatty acids	Increased free fatty acids
Increased amino acids	
Starvation	Obesity
Sleep	IGFs
Exercise	Senescence
Stress	Growth hormone
Puberty	
Estrogens	Progesterone
Androgens	Glucocorticoids
α-adrenergic agonists	β-adrenergic agonists
Serotonin	Serotonin antagonists
Dopamine agonists	Dopamine antagonists
Thyrotropin-releasing hormone	Tamoxifen

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