It is well known that somatotrophin or human growth hormone (hGH) secretion declines significantly in healthy individuals during aging, contributing to increased central obesity, reduced muscle mass and bone mineral content, as well as to decay of psychological perception of well being (Rosen et al, 1993). This age-associated deficiency is sometimes called the somatopause. By causing maladaptive changes in body composition and metabolism, progressive hGH insufficiency also increases the risk for development of intrinsic diseases of aging that are the common cause of death after the age of 50 years. However, expanding knowledge of neuroendocrine function and how it may be modulated with pharmacological agents brings enthusiastic support for the use of such molecules to prolong health and vitality in the elderly. Heretofore, recombinant hormone growth hormone was used to replace declining concentrations of the naturally occurring molecule. While this approach was effective in reversing certain somatic and metabolic deficiencies associated with the somatopause, it lacked the ability to simulate naturally occurring profiles of hGH secretion that are an essential part of its action, and the pharmacological approach brought with it the possibility of side effects and abuse. Thus, more effective and desirable methods for opposing effects of the somatopause would be to restore waning functions within the neuroendocrine system by specifically targeting the pituitary gland. This holistic approach would not only meet the objective of reversing age-related growth hormone insufficiency, but would avoid the undesirable effects previously mentioned since feedback relationships would prevent excessive release of the hormone.

Approaches for achieving holistic interventions to improve hGH secretion and promote pituitary recrudescence during aging derive from an understanding of how the neuroendocrine system is regulated in youth. Regulation of hGH secretion had become the focus of early hormone research with the pioneering observation of Reichlin that surgical destruction of the ventromedial nucleus within the hypothalamus slowed growth velocity (Reichlin, 1960). As other hypothalamic regulatory factors were being discovered during the late 1960's and 1970s, an inhibitory hormone called somatostatin (SS) capable of blunting GH secretion was identified. At that time, it was suggested that SS was the sole hypothalamic regulator of GH secretion exerting negative control over its release (Brazeau et al, 1973). However, that concept did not fit the experimental and clinical evidence so that search for a stimulating agent was initiated. This quest resulted in the identification and sequencing of growth hormone releasing hormone (GHRH) approximately ten years after the discovery of SS. The identification and structural sequencing of GHRH represented a deviation from the rule that hypothalamic factors be isolated from animal tissues. In fact, GHRH was first found in humans and not in their brain tissues, but rather in pancreatic islet tumors that caused hGH hypersecretion and acromegaly (Zafar et al., 1979; Rivier et al., 1982; Guillemin et al., 1982; Frohman and Downs, 1987). This discovery proved to be fortuitous for determining structure/activity relationships of GHRH because it provided a relatively abundant source of study material compared with that which could be extracted from brain tissue. A 40 amino acid peptide designated human pancreatic growth hormone releasing factor, hpGRF-(1-40) was isolated from one of the two pancreatic tumors, while three others including GHRH-(10-44)-NH2 , GHRH-(1-40)-OH, and GHRH-(1-37)-OH were sequenced from the other tumor (Rivier et al., 1982). Two of the three GHRH forms (GHRH-(10-44)-NH2 , GHRH-(1-40)-OH) found in the pancreatic tumors were subsequently identified in human hypothalamic tissues differing in structure only by the absence of the latter four COOH-terminal amino acid residues (Ling et al, 1984). Structure-activity relationships showed that the NH2 -terminal 29 residues of GHRH-(1-40)-OH have biological activity and indicated that while the NH2 -terminal portion of the molecule is involved in binding to the receptor, the COOH terminus is responsible for determining the potency of the molecule. Based upon this information, the synthetic analog, GRF1-29 NH2 or sermorelin was subsequently developed for clinical applications.
Because of its distribution in the body, GHRH has been identified as belonging to an expanding family of brain-gut peptides that interestingly include another pituitary stimulating agent called ghrelin. Interestingly, ghrelin was discovered only within the past decade although its existence was implied by a number of synthetic molecules called GHRP's or GH releasing peptides that were created in the 1970's. These originated when the search to identify and sequence GHRH was well under way. Rather than extracting and fractionating brain tissues to identify those with hGH releasing activity, a reverse strategy was employed in which the investigators used and modified structures of known neuroactive peptides hoping to find a hGH secretagogue. The first GHRPs were discovered upon derivitization of the pentapeptide, metenkephalin an opioid peptide (Bowers et al. 1977). The initial molecule known to be active as a hGH secretagogue was Tyr-D-Trp-Gly-Phe-Met-NH2 which had poor activity but served as a model from which the new category of GHRPs were designed. The evolution of this lineage is presented below which describes the sequential development from the prototype, GHRP-6 to the most recent, GHRP-2.

(From Muller et al, 1999)

Figure 1. Structural evolution of growth hormone releasing peptides (GHRP’s), the synthetic analogs of ghrelin, a naturally occurring molecule known to affect pituitary somatotrophic functions as well as those of other vital tissues and organs. Sequence begins with D-trp-metenkephalin and ends with the hexapeptide, GHRP-2, the most potent peptide of the series.
GHRP-6 was the first hexapeptide with strong hGH releasing activity in vivo, especially in human beings (see Muller et al., 1999). Subsequently, more potent analogs such as GHRP-2 were developed and their receptors on pituitary somatotrophs characterized and shown to be different from those for GHRH. Based upon the existence of such specific receptor that were distinct from GHRH, the search for an endogenous ligand was undertaken. Finally, in 1999, more than 20 years after the discovery of GHRPs, ghrelin was discovered in the stomach although its distribution in other tissues has been described as is shown below (see van der Lely et al., 2004).

Figure 2. Multiple loci of action of ghrelin, a naturally occurring 28 amino acid peptide with potent hGH stimulating activity. Ghrelin represents the natural ligand for the GHRP receptors that are activated separate from those of GHRH during therapy to oppose the somatopause.

The discovery of ghrelin a unique example of reverse pharmacology in which discovery of an unknown ligand for a regulatory peptide receptor was preceded by synthesis of analogs (GHRP) from which the natural receptor was characterized.

Thus, we currently understand that hGH is regulated by a complex network of neural and endocrine factors that ultimately are expressed through two main hypothalamic regulators and one ancillary factor. The two primary neurohormones are GHRH and somatostatin (SS). These exert direct stimulatory and inhibitory influences, respectively upon somatotropes, while the GHRPs modulate their effects on these specific pituitary cells responsible for production and release of hGH. In particular, GHRPs
enhance the stimulatory effect of GHRH while opposing the inhibitory influences of somatostatin. For example, while GHRP and GHRH stimulate hGH secretion and equally attenuate the inhibitory actions of SS, the combination of GHRH and GHRP are synergistic. This results in significant amplification of instantaneous GH secretion and enhancement of its pulsatile release. These differences are shown below.

Comparative effects of combined and individual doses of GHRH and GHRP

![Graph showing comparative effects of combined and individual doses of GHRH and GHRP](image)

(from Bowers et al., 2004)

**Figure 3:** Comparison of responses to individually administered GHRP or GHRH with those resulting from their combined administration. Note the age differences as well as the potency differences of the individual and combined neuropeptides as indicated by the amplitudes of growth hormone release represented in columns 1 and 4. These are approximately the same even though the dose of GHRP in column 1 is one tenth of that in column 4.
As is obvious in Figure 3, there is a significant difference in the response of young and older individuals to the initial administration of the hGH secretagogues. Indeed, age desensitizes the pituitary to secretagogue action resulting in less hGH being release. However, it also reduces the pattern of hGH secretion which is youth is represented by intermittent, high amplitude episodes of GH release into the blood.

Growth hormone secretion is markedly pulsatile in all species studied (see Muller et al., 1999). This pattern is necessary for hGH efficacy since it has been shown that constant exposure to the hormone as would be experienced by administration of recombinant hormone, is less capable of eliciting beneficial physiological responses in animals and humans than is intermittent administration. Relevant to this point is the fact that the 24-hour pattern of spontaneous GH release becomes blunted with age such that it eventually ceases. These changes account for the age-related decline in pituitary GH production and secretion. On the other hand, secretagogues amplify naturally occurring pulsatile GH secretion and that the combination of GHRH and GHRP is most effective in this regard (Figure 4). As a result, their combined use is indicated for rejuvenation of the pituitary during aging and thereby for opposing hGH insufficiency associated with the somatopause.

(From Bowers et al., 2004)

Figure 4. Graphic representation of the effects of GHRH alone or in combination with GHRP at different doses administered to older men and women. Each individual row represents a 24 hours period for each gender receiving different doses and combinations of the secretagogues. Changes in IGF-1 over the 24 hours period are expressed for each subject. Note the dramatic increases in pulsatile hGH secretion resulting from combinations of GHRH and GHRP and also that GHRP is approximately 10 times as potent as GHRH when administered separately.
In conclusion, this brief overview of the history and applications for receptor-specific hGH secretagogues is intended to define their properties so as to distinguish them from non-specific secretagogues often used unsuccessfully to treat symptoms of the somatopause. More importantly, it is intended to underscore the greater safety and efficacy of sermorelin and GHRP combinations in providing a more physiological and holistic approach to restoring benefits of endogenous hGH that progressively declines with advancing age contributing decay of form and function. It is important to remember that unlike recombinant hGH, which stimulates production of the bioactive hormone IGF-1 from the liver, the receptor specific secretagogues simulate the patient’s own pituitary gland to increase production and secretion of endogenous hGH. Because of this unique action combinations of sermorelin and GHRP have distinct advantages over recombinant hGH that include the following:

- The stimulatory effects of sermorelin and GHRP are regulated by negative feedback from the pituitary and brain so that overdoses of hGH are difficult if not impossible to achieve thereby avoiding side effects and the potential for abuse.
- Tissue exposure to hGH released by the pituitary under the influence of sermorelin and GHRP is episodic not “square wave” so as to simulate youthful endocrine function and prevent tachphylaxis.
- By stimulating the pituitary sermorelin and GHRP rejuvenates the growth hormone neuroendocrine axis that is the first to fail during neuroendocrine aging. This effect opposes the age-associated cascade of pituitary failure thus maintaining integrity of the other important hormone systems, e.g., thyroid, adrenal, reproductive, etc.
- Pituitary recrudescence preserves not only youthful endocrine physiology but also its beneficial effects on anatomy and somatic integrity, i.e., body composition et al.
- It provides the patient with all the benefits and more of hGH replacement therapy without violating federal restriction on the prescribing of recombinant hGH.
Dosing of GH secretagogues should be titrated to meet the needs of each patient. Though it may seem obvious, age, gender, body type, personality and other variables will affect outcomes of this therapy. The following are intended as general guidelines for secretagogue therapy that will be modified by the physician to maximize the benefits of each of his/her patients. The following considerations should be taken into account.

1. Age: In general, therapy should not be initiated in healthy individuals under the age of 40 years. During the 40’s the need for GHRH (sermorelin) as a primary stimulus is not significant. Instead, the potentiating effect of GHRP will be of greater value in sustaining normal function of the GH neuroendocrine axis for as along as possible. Also, since younger individuals require less support than older ones, the weaker GHRP, i.e., GHRP-6 may be quite effective in the younger patient. Thus, daily combination therapy of sermorelin (0.2 ug) + GHRP-6 (1 mg) or sermorelin (0.2 ug) + GHRP-2 (0.5 mg) should suffice. For older individuals, increasing amounts of sermorelin may be used so as to replace the progressive deficiency of the GHRH neuropeptide with each advancing decade of life. In any event, for each patient, dose titration should be considered within a month of starting therapy. After 30 days on therapy, IGF-1 measures will provide an index of accuracy for initial dose selection. While objective clinical criteria such as reduced total body/visceral fat or increased lean body mass will not be significantly altered during the first month, subjective opinions of the patient should be considered since “feelings” of energy, endurance, libido or other indicators of life quality may be affected. Should more stimulation be required, then upward adjustment to combinations of the three secretagogues, including sermorelin, GHRP-6 and GHRP-2 at doses previously identified may be used. With advancing age and in those who are particularly refractory to pituitary recrudescence, increases in dosage to maxima of 1, 2, 1 milligrams of sermorelin, GHRP-6 and GHRP-2, respectively may be tried until an effective and safe maintenance dose has been achieved.

2. Gender: While estrogen tends to blunt women’s responses to hGH, females are more sensitive to secretagogues and especially combinations of sermorelin and GHRP’s. Thus, older women who are not overweight or obese may be started on doses of the combination secretagogues that are used in therapies for younger men, i.e., in the 40 + year range. As before, these doses may be increased depending upon serum IGF-1 concentrations, clinical markers and subjective comments of each patient. Attentions should be paid to patient comments especially regarding references to the reproductive function. In some perimenopausal women, improved ovarian function may increase chances of unwanted pregnancy so that they should be advised of this possibility. Also, FSH levels may be monitored to further evaluate reproductive function in the perimenopausal group.

3. Obesity: Overweight and obese subjects tend to be more refractory to secretagogue therapy than leaner ones. Thus, initial dosing may employ higher combinations of all three secretagogues i.e., sermorelin (1mg), GHRP-6 (1 mg), GHRP-2 (1 mg).

Comments and clinical considerations: Because individuals respond differently, physicians should intermittently monitor progress of each subject. Depending upon cost, laboratory tests should include at least IGF-1. Since thyroid function has been found to be altered by the hGH secretagogues (feedback improved and bioactive hormone increased) a thyroid panel may be useful. As previously suggested, FSH may be measured in perimenopausal women and testosterone also, since it is increased, especially in men on therapy. Safety measures should include PSA and serum insulin (as a means to monitor age-related insulin resistance). Also, a lipid panel will provide metabolic information for comparing with clinical measures of total body and visceral fat as well as lean body mass (impedance measures). Forced vital capacity is simple to measure and provides a good biomarker of efficacy in reversing maladaptive changes of aging over the long term. Patients should be asked to keep a diary in which experiences should be recorded and reported to the physician, whether or not they seem to be relevant to the treatment. Such information provides a broad overview of effects, indicators of possible side effects and a means for the physician to better understand the short and long term outcomes of patients on secretagogue therapy.

For more information, please contact Royal Palm Compounding Pharmacy at 1-877-784-0702.
REFERENCES


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