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Treating age-related changes in somatotrophic hormones, sleep, and cognition

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Abstract

Many of the body's systems that function to maintain optimal health and well-being decline with advancing age. Aerobic capacity, muscle mass, and strength all progressively decline. Significant sleep disturbances are associated with increases in morbidity and mortality. Cognition declines, impacting an older individual's ability to function independently. Interventions that could at least stabilize or possibly improve functional capacity, sleep quality, and cognitive function have the theoretical potential to prolong an older individual's ability to live independently, and interest in their possible utility is growing rapidly. One such intervention may be stimulation of the “somatotrophic” axis via growth hormone-releasing hormone (GHRH). Here we review the evidence for such somatotrophic interventions. We also report preliminary findings on the effects of chronic GHRH treatment on the somatotrophic hormones, body composition, functional status, sleep, and cognitive function of healthy older men and women from two major GHRH intervention studies, one recently completed and the other ongoing.

Keywords: *aging*, *cognition*, *growth hormone-releasing hormone (GHRH)*, *chronic GHRH treatment*, *sleep*, *somatotrophic hormone*

Many of the body's systems that function to maintain optimal health and well-being decline with advancing age. Aerobic capacity, muscle mass, and strength all progressively decline with age. This loss of muscle mass, or sarcopenia, and the accompanying reduction in strength increase the risk of falls and their complications, and for many individuals the associated loss of physical functional capacity leads to increasing difficulty in living independently. Complaints of poor sleep are common in older populations. Insomnia reduces quality of life and is often a factor in decisions to seek health care.

Sleep complaints often lead to overmedication and sedation of the elderly, with the numerous potential attendant problems, including increased morbidity and mortality. Finally, cognition also declines with advancing age, particularly those cognitive functions that involve novel problem solving and psychomotor processing speed, with its own related impact on the older individual's ability to function independently.

Interventions that could at least stabilize or possibly improve functional capacity, sleep quality, and cognitive function theoretically have the potential to prolong an older individual's ability to live independently, and interest in their possible utility is growing rapidly. There is increasing evidence that the functioning of many of these systems may be improved through stimulation of the “somatotrophic” or growth hormone (GH)-insulinlike growth factor-I (IGF-I) axis. Levels of GH and IGF-I rise rapidly at puberty, remain high during early adulthood, and then decline progressively with aging. It has been suggested that with age there is a “somatopause” of GH-IGF-I anabolic status in both sexes, which is reversible by GH restoration or stimulation therapies. Because the aging pituitary remains capable of synthesizing and secreting increased amounts of GH if appropriately stimulated, several recent studies have examined the effects of administering GH secretagogues (GHSs) - factors that stimulate GH secretion - as an alternative to GH treatment. These secretagogues include analogs of the endogenous hypothalamic GHS, growth hormone-releasing hormone (GHRH).

Here we briefly review the evidence for such somatotrophic interventions. We also report preliminary findings on the effects of chronic GHRH treatment on the somatotrophic hormones, body composition, functional status, sleep, and cognitive function of healthy older men and women from two major GHRH intervention studies, one recently completed and the other ongoing.

Aging, somatotrophic hormones, and body composition

GH is secreted by the pituitary under the hypothalamic control of at least three peptide systems: somatostatin (somatotropin-rcleasc inhibiting factor [SRIF]), which inhibits GH secretion; GHRH; and a second recently characterized secretogogue, ghrelin.[1] The combined influences of these systems yield a pulsatile pattern of GH secretion in peripheral blood. GH exerts its effects by binding to its own receptor as well as by stimulating the synthesis of IGF-I. The liver is the primary contributor to levels of IGF-I in the systemic circulation, but IGF-I is generated in many GH target tissues, and local effects may be more important than those of circulating IGF-I of hepatic origin.[1]

With aging, there are declines in the GH-IGF-I axis[2] and in lean body mass.[3] The amplitude of stimulated GH release as well as integrated 24-hour GH levels have been observed to decline with age.[4-8] Parallel declines in IGF-I have also been observed by ourselves and others.[4,9,10] A variety of mechanisms could potentially underlie this decline in GH secretion with aging. Current evidence suggests that this is most likely the result of both a decrease in GHS activity and an increase in somatostatin, but not an intrinsic loss of pituitary capacity to secrete GH. Consequently, stimulation of the somatotrophic axis with GHRH is a potential alternative to replacement with GH itself in normal aging. GHSs such as GHRH may result in a more “physiological” stimulus to GH secretion than GH per se. GHRH yields a pulsatile GH secretion as opposed the continuously elevated levels seen with GH administration. Further, when a secretogogue is used, the normal negative feedback regulation by IGF-I on pituitary GH secretion is preserved, offering the possibility of reduced side effects.

The hypothesis that age-related decreases in IGF-I and protein synthesis are due to an age-associated decrement in GH secretion is supported by studies showing that exogenous GH administration restores plasma IGF-I to youthful levels in aged animals and humans.[11-13] Similarly, IGF-I restores protein synthesis and lean body mass (LBM) in animals and humans.[11,14,15] Thus, the age changes in the GH-IGF-I axis and LBM appear to be at least partly reversible.

Aging, sleep and somatotrophic hormones

Nearly 40% of the older (over 55 years) population suffers from and complains of insomnia, fragmented sleep, and poor sleep quality, more than any other age group.[16-19] Older individuals are twice as likely to complain of difficulties falling asleep and remaining asleep, and of having less restful sleep than younger individuals. These complaints of poor sleep are supported by objective findings in the sleep laboratory, which include: (i) a decrease in stages 3 and 4 sleep (slow-wave sleep [SWS]), often called "deep" sleep, and the delta electroencephalography (FRG) activity that characterizes it; (ii) an increase in the number of awakenings from sleep and an increase in the total time spent awake; and (iii) a decrease in the rapideye-movement (REM) sleep stage. We[20,21] and others have shown that these disturbed sleep patterns are seen even in optimally healthy, noncomplaining, elderly individuals who have been carefully screened for possible medical and psychological factors that might disrupt sleep.

The public health burden associated with sleep disturbances in the elderly is considerable. These sleep disturbances have been linked to increased use of sedative hypnotics,[22-5] greater use of the health services,[22,26-28] and reduced functional ability and quality of life.[17,18,29,30] Further, these sleep disturbances are frequently comorbid with physical and mental illness,[22,28,31-34] are often a major reason for nursing home placement,[35,36] and may predict future declines in physical health and mortality.[35,37-42] The consistent report of disturbed sleep[16,43] by the elderly may account for the disproportionate prescription of sedative hypnotics to the elderly population.[16,15] Hypnotic medication offers only short-term efficacy and, in the long term, may itself disrupt sleep.[44,45] Hypnotic use may also lead to exacerbation of sleep apnea and daytime carryover effects, such as sedation, delirium, falls, fractures, cognitive impairment, and anterograde amnesia[46] and has been associated with increased morbidity and mortality.[35,37-42] The 1991 National Institutes of Health (NIH) Consensus Conference on the Treatment of Sleep Disorders of Older People concluded that "nonsedative hypnotic approaches to improve sleep quality in the elderly population are sorely needed."[19] Pulsatile GH secretion continues with aging, but with a pattern of diminished GH pulse amplitude.[4] In particular, nighttime GH secretion declines, so that there is often no longer a clear night-day GH rhythm. SWS also declines with aging, although it is unclear whether the GH decline is due to the reduction in SWS, whether SWS deteriorates because of the decline in GH, or whether both arc decreased because of a common reduction at a higher level of regulation (eg, GHRH). Recent studies have shown that sleep is influenced by clinical extremes of GH status[47,48] and that sleep can be improved in response to acute GH administration[49] or stimulation of the GH-IGF-I axis using GHRH.[50] Acute GHRH administration increases SWS[51] and acute decreases in GH status by a GH-releasing factor antagonist decrease slow-wave amplitude and SWS duration[52] in animals. Among hormones, GHRH displays the bestdocumented sleep-promoting activity and is clearly implicated in the regulation of sleep, specifically non REM sleep. GHRH hypothalamic neurons projecting to the basal forebrain, specifically the medial preoptic area, likely act directly to increase non-REM/SWS.[53] Three independent laboratories have recently reported that GHRH promotes sleep in healthy young subjects,[54-58] although two older studies reported no such effect[59,60] and there is some evidence to suggest that the impact of GHRH on the sleep of the elderly may be weaker.[61,62]

Aging, cognition, and somatotrophic hormones

While it has been extensively documented that significant changes in several major areas of cognitive function develop with advancing age, such declines do not develop uniformly. For example, some components of memory remain relatively intact with advancing age (eg, primary or shortterm memory) , while others do not (eg, secondary or longterm memory). A major distinction that is useful for describing those functions that are preserved versus impaired by advancing age was proposed by

Cattell, ie, the concepts of crystallized versus fluid intelligence.[63] Crystallized intelligence, or abilities dependent upon accumulated experience and education, such as general knowledge, culture-specific rules, and formal verbal reasoning, arc relatively resistant to age-related decline. Conversely, fluid intelligence, or abilities involving concept formation, rule discovery, planning behavior, and nonverbal reasoning, markedly decline with advancing age. Recently, Salthouse and others have suggested that this age-related change in fluid intelligence is at least partially the result of decreases in mental processing speed.[64,65]

It has been suggested that the declines in GH and IGF-I observed with advancing age may contribute to the impaired cognitive function associated with aging and perhaps to that seen in neurodegenerative diseases such as Alzheimer's disease.[66-70] GH and IGF-I arc present in the cerebrospinal fluid and both have binding sites in the central nervous system (CNS), particularly in the hippocampus, a brain structure crucial to learning and memory.[71-73] Significant negative correlations have been observed between advancing age and the density of GH binding sites, particularly in the pituitary, hypothalamus, and hippocampus.[74,75] We and others have reported positive correlations between IGF-I and cognition in the healthy elderly.[76,77] Further, impairments in cognitive function have been reported in adults with either childhood- or adult-onset GH deficiency.[78,79] Finally, two recent, placebo-controlled trials[80,81] of 6 to 24 months of GH treatment in GH-deficient adults reported improved cognitive function with GH replacement. However, it should be noted that a third, similar, placebo-controlled study[82] observed no such improvement after 18 months of GH treatment.

Chronic GHRH treatment; preliminary results

Taken as a whole, the literature reviewed above suggests that augmenting the somatotrophic axis with chronic GHRH may have an impact not only on GH, IGF-I, body composition, and therefore physical function status, but also on CNS function, specifically sleep quality and cognitive function. At the University of Washington, we have been conducting two NIH-supported studies of the effects of chronic GHRH administration on hormonal and functional end points in healthy older women and men. One recently completed study (grant number ROl AGI 0943 to R. S. Schwartz) assessed the combined effects of 6 months' treatment with GHRH or placebo and an exercise intervention on body composition, strength, and functional status in healthy older women not taking estrogen replacement therapy. The second, ongoing study (grant number R01-MH53575 to M. V. Vitiello) examined the effects of 5 months' treatment with GHRH or placebo on GH profiles, body composition, and functional status including sleep, cognition, and physical function in healthy older men and women; this trial is still in progress. Both studies involved the same drug treatment: a single evening subcutaneous injection of GHRH (14 μg/kg [≈1 mg] of GHRH(1-29)NH2, sermorclin acetate, Gcrcf®, Scrono Laboratories Inc). Because both of these studies involve women on estrogen replacement therapy (RRT) and women not on estrogen replacement therapy (NERT) as well as men, it will ultimately be possible to examine not only gender but also estrogen replacement status effects on the impact of GHRH treatment. While one of these studies is still ongoing and only preliminary results from both studies have been reported to date, a few early, tentative conclusions can be offered.

Somatotrophic hormones, body composition, and physical function

These studies show that once -nightly doses of GHRH are well tolerated and can significantly enhance GH secretion and elevate IGF-I levels. They also demonstrate differences in responses among gender/estrogen replacement groups, and limitations in current GHRH formulations. The side effects typically reported in GH treatment studies, mainly peripheral edema and arthralgias, were very uncommon. Rarely, GHRH-treated patients reported ery thema or swelling at the injection site. Male subjects doubled their 24-h GH secretion and experienced a 40% rise in IGF-I levels.[83] NERT women

had a similar response, with an average 30% increase in IGF-I levels over baseline. RRT women had the most vigorous increase in GH in response to GHRH, but, despite this, they experienced the lowest IGF-I increments, averaging <10%. These results suggest that oral estrogen replacement induces relative GH resistance. This last result is comparable to that reported in estrogenized vs nonestrogenized adult patients with GH deficiency receiving GH replacement.[84] While the significant increase in GH was maintained for the duration of the treatment period, there are clear limitations with the current GHRH formulation. A single, large burst of GH secretion was observed immediately following each evening injection. Nighttime pulsatile GH secretion was not restored. Further, late-night GH secretion was reduced compared with baseline GH profiles. This could represent a temporary exhaustion of releasable GH stores following the acute supraphysiological effect, or negative feedback suppression by the increased circulating levels of IGF-I. Daytime GH secretion, while still low, was not suppressed, favoring the former explanation. The net effect of GHRH treatment is the observed near-doubling of overall GH secretion and a ≈40% increase in IGF-I.

Body composition measured by whole -body dual energy x-ray absorptiometry (DEXA) scans shows a significant decrease (≈5%) in percentage body fat in men and NERT women, with a reciprocal increase in LBM.[83,85,86] As with the effect on IGF-I, the GHRH effect on body composition is blunted in ERT women; it appears that oral estrogen induces a resistance to GH action. This blockade is qualitatively similar to the effect seen in ERT GH-deficicnt women receiving GH treatment.[84]

In these studies, physical function was assessed by both standard measures of strength and a continuous-scale physical functional performance (PFP) test developed at the University of Washington.[87] The PFP is designed to assess the higher capabilities of subjects living independently and it has been shown to measure deterioration in physical function, which was not clinically apparent, over a 6-month period. PFP results for the current studies are very preliminary. The effects of GHRH appear to vary by specific task, some showing improvement in the actively treated group and no change in those receiving placebo, while others show no change with GHRH and deterioration with placebo.[85,88]

Sleep quality and cognitive function

Both objective and subjective sleep arc being measured in the ongoing NIMH-funded study; however, preliminary data are currently available only for subjectively rated sleep quality. The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, which assesses sleep quality and disturbances over a 1 -month time interval. Nineteen individual items generate seven “component” scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.[89] The sum of the scores for these seven components yields one global score with a maximum possible score of 25. A global PSQI score greater than 5 has been shown to significantly distinguish good and poor sleepers, although this criterion was not developed on older subjects where higher scores are to be expected. Counterintuitively, GHRH treatment was associated with a very small but significant increase in PSQI total score (4.1±2.8 vs 5.41±2.8, N=37, $P<0.05$) suggesting that chronic GHRH resulted in poorer sleep. No change in PSQI was noted for the placebo group (4.51±2.9 vs 4.61±2.7, N=38). Examination of the PSQI's seven component scores within the GHRH group revealed no clear impact of GHRH treatment on any of the components, suggesting that this may be a nonspecific finding. The real significance of this small increase in subjectively rated sleep quality remains unclear and awaits analysis of the full study sample and the corresponding analysis of objective sleep measures.

We and others have reported positive correlations between IGF-I and cognition in the healthy elderly.[76,77] In a previously published abstract of a study in 64 patients,[90] we reported that GHRH treatment resulted in significantly improved performance (5% to 7%) relative to placebo on several

cognitive tasks, particularly those involving psychomotor and perceptual processing speed. The pattern of results observed in the larger group of 75 patients, which we reported at the 2000 Meeting of the Gerontological Association of America, supports this initial, tentative conclusion and further indicates that the beneficial impact of GHRH treatment may be observed in other cognitive tasks that are less dependent on processing speed. On the basis of the findings of this larger, but still incomplete sample, we conclude that 5 months of daily GHRH treatment may have a small, but significant, beneficial effect on the cognitive abilities of healthy older men and women. These preliminary findings support the hypothesis that the age-related declines in the somatotrophic axis may be related to declines in cognition, and that supplementation of this neurohormonal deficit may partially ameliorate such cognitive deficits.

Summary of study on chronic GHRH treatment

Overall, it appears that once-daily GHRH injections can stimulate the desired increases in GH and IGF-I and result in significant increases in LBM and declines in fat mass, although these results are tempered by estrogen status in women. Alone, however, they do not support an indication for treatment unless these increases induce meaningful changes in muscle mass and functional capacity and other outcome measures. While GHRH treatment produced a single large burst of GH secretion immediately following each evening injection, a “youthful” nighttime pulsatile GH secretion pattern was not restored. This increase in overall GH and IGF-I levels may suffice for some effects mediated through GH and IGF-I (eg, changes in body composition and possibly improvements in cognitive function), but it is far from a restoration of nighttime pulsatile GH secretion, which may be required to support any possible beneficial effects on sleep quality. For this, a sustained-release formulation or an analog with a duration of action of at least 8 h will be needed. It must be emphasized that these conclusions regarding the effects of GHRH treatment are tentative, as more definitive results will not be available until both studies are completed and analyzed.

Conclusions

Our preliminary results show that once-daily evening subcutaneous injections of GHRH are well tolerated and can increase 24-h GH secretion, boost circulating levels of IGF-I, and improve body composition in older patients. Preliminary analyses also suggest beneficial effects on physical and cognitive performance. These findings, while encouraging further study, are far from the type of results that can support use of GHRH to “treat” aging.[1,91] As aging is not a disease, drug therapy cannot be encouraged until meaningful functional benefits are shown either in treatment or in the prevention of specific disorders associated with aging. The recent preliminary report of a multicenter European study showing that GH may accelerate recovery from hip fracture[92] is an example of such a finding. Nevertheless, the observed beneficial effects of GHRH and its minimal side effects are encouraging and indicate that future work in this area is well worth pursuing with the hope of ultimately improving the overall health and quality of life of the seniors, who currently represent the fastestgrowing segment of our population.

Selected abbreviations and acronyms

GH	growth hormone
GHRH	growth hormone-releasing hormone
GHS	growth hormone secretagogue
IGF-I	insulinlike growth factor-I
LBM	lean body mass
REM	rapid eye movement
SWS	slw-wave sleep

Notes

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