Growth hormone releasing hormone improves the cognition of healthy older adults

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Received 25 August 2004; received in revised form 13 December 2004; accepted 7 January 2005

Abstract

Declines in the activity of the somatotrophic axis have been implicated in the age-related changes observed in a number of physiological functions, including cognition. Such age-related changes may be arrested or partially reversed by hormonal supplementation. We examined the effect of 6 months treatment with daily growth hormone releasing hormone (GHRH) or placebo on the cognition of a group of 89 healthy older (68.0 ± 0.7) adults. GHRH resulted in improved performance on WAIS-R performance IQ (p < 0.01), WAIS-R picture arrangement (p < 0.01), finding A's (p < 0.01), verbal sets (p < 0.01) and single–dual task (p < 0.04). GHRH-based improvements were independent of gender, estrogen status or baseline cognitive capacity. These results demonstrate that the age-related decline in the somatotrophic axis may be related to age-related decline in cognition. Further they indicate that supplementation of this neuro-hormonal axis may partially ameliorate such cognitive declines in healthy normal older adults and potentially in individuals with impaired cognitive function (i.e., mild cognitive impairment and Alzheimer’s disease).

Keywords: Aging; Elderly; Cognition; GHRH; GH; IGF-I; Cognitive function

1. Introduction

It has been suggested that the declines in growth hormone (GH) and insulin-like growth factor I (IGF-I) observed with advancing age may contribute to the impaired cognitive function associated with aging [2,17,26] and perhaps to that seen in neurodegenerative diseases such as Alzheimer’s disease [4,5,9]. GH and IGF-I are present in the plasma and the cerebrospinal fluid, and both have binding sites in the CNS, including in the choroid plexus and particularly in the hippocampus, a brain structure crucial to learning and memory [1,8,14]. Significant negative correlations have been observed between advancing age and the density of GH binding sites, especially in the pituitary, hypothalamus and hippocampus [10,15].

Sonntag has recently reviewed the interactions of GH, IGF-I and brain aging [21,22]. He noted that studies in aged rodents have demonstrated that administration of GH, IGF-I or GHRH results in: (1) increased cortical microvascular density and inferred cerebral blood flow [23]; (2) increased cortical glucose metabolism [12]; (3) amelioration of age-related declines in hippocampal neurogenesis [11]; and (4) reversal of age-related declines of spatial and reference memory [24,25].

GH deficient (GHD) children have significant cognitive deficits, which may be moderated by GH treatment [19,27]. Cognitive deficits are also seen in GH deficient adults.
and can be normalized by GH therapy [7,20]. Several studies have reported positive correlations between IGF-I and cognition in the healthy elderly [2,18,28], particularly those involving processing speed. While there have been no previous direct examinations of the effect of GHRH treatment on cognitive function, aside from the current study, the effect of somatotropic axis supplementation by GH treatment has been explored. Three recent, placebo-controlled trials [7,16,18] of GH, rather than GHRH treatment, of 6–24 months duration in GHD adults reported improved cognitive function; although a fourth, similar, placebo-controlled GH treatment study [3] observed no such improvement after 18 months of treatment.

Given the emerging evidence in support of the likelihood that stimulating the somatotropic axis can influence cognition, an obvious and important question that the current study seeks to answer is whether somatotropic supplementation can improve cognitive function in healthy older adults. The current study employs GHRH rather than GH to augment the somatotropic axis. This use of GHRH has several advantages [13]. For one, GHRH, depending on its exact formulation, produces either a brief pulse of GH secretion, or a train of pulses, generally resembling physiological pulsatile GH secretion, rather than a prolonged rise in GH levels as seen with GH supplementation. This is important since, in other contexts, the pattern as well as the quantity of GH delivered has been found to modulate its effects. Also, when a secretagogue such as GHRH is used, the normal negative feedback regulation by IGF-I on pituitary GH secretion is preserved, offering at least some relative buffering against overdosing. Thus, GHRH provides a more “normal physiologic” boost to GH secretion than GH itself, which is potentially important in any study population but perhaps more so in the senior population where somatotropic axis activity is compromised [13].

Here we report the results of a prospective, randomized, placebo-controlled, double-blinded study of the effects of 6 months of GHRH treatment on the cognitive function of healthy older men and women.

2. Methods

2.1. Subjects

Subjects were normal, healthy, non-smoking men and women between the ages of 60 and 85. They were taking no major medications except for stable thyroid replacement and peripheral anti-hypertensives, and no “cognitive enhancing” drugs, herbs or supplements including Ginkgo biloba. Potential subjects with obesity, diabetes, uncontrolled hypertension, known pituitary disease, carpal tunnel syndrome, debilitating arthritis, pulmonary, major cardiovascular disease, dementia, psychiatric disease or sleep disorders, were excluded. Individuals with a personal (or strong family) history of breast cancer (for women), prostate cancer (for men) or colon cancer (or multiple colon polyps), were excluded. All subjects had a normal screening mammogram (for women) or PSA (for men) within 1 year of study entry.

Subjects were recruited from the Greater Seattle area through advertisements in various local media and brochures distributed at senior centers, residences and events. Subjects were recruited to participate either in a research project examining GHRH effects on GH, sleep quality and body composition in healthy older women on estrogen replacement therapy and healthy older men (RO1 MH53575, MVV); or a research project examining the impact of GHRH and exercise training on strength, body composition and physical function in healthy older women not on estrogen replacement therapy (RO1 AG10943, RSS). No mention of cognitive function was made in advertisements for either project.

Subjects were initially screened for major inclusion/exclusion criteria over the phone. This was followed by a history and physical examination, screening laboratory tests and an ECG at the UWMC’s General Clinical Research Center (GCRC).

One hundred subjects entered the study and were randomized to either GHRH or placebo, 89 (89%) completed the study. Eleven subjects were excluded or dropped out of the study: two (2%) for reasons likely related to the study drug protocol (one with urticarial rash at the site of injection and one with a general feeling of malaise after starting injections); and nine (9%) for reasons not likely related to the study drug protocol (one who moved away, one claimed the study required too much time commitment, one with a retinal aneurysm, one with a nasal hemorrhage, two who were uncomfortable with the daily self-injection procedure, one with bladder cancer, and one who was uncomfortable with the sleep recording protocol, a part of the parent study).

2.2. Procedures

The University of Washington Institutional Review Board approved the study and all participants provided written informed consent in advance of their participation. These procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Except where noted, all procedures were performed at the University of Washington GCRC.

All subjects underwent baseline (T1) and 6 months/treatment (T2) cognitive testing on the second day of each of two 72 h stays on the GCRC. During each of their stays on the GCRC the subjects ate a weight stabilization diet, similar to the Phase 1 diet recommended by the American Heart Association.

Beginning immediately after their T1 assessment, subjects were randomized to GHRH or placebo and began self-injection of GHRH (1–29) NH2 (sermorelin acetate, GEREF®, Serono Laboratories Inc.) or placebo SC for 6 months. All subjects were carefully instructed on sterile technique for mixing diluent into the drug vials and subcutaneous injection. The GHRH subjects began self-injection of 1 mg (∼14 μg/kg) of drug in 1 ml of diluent ∼1 h prior to bedtime. The placebo subjects injected a like amount of
placebo. Subject logs and return of used drug vials indicated a self-injection adherence rate of 98.4%.

A single, un-blinded investigator (GRM) monitored IGF-I levels of both groups. If, after 2 weeks of injections, the IGF-I levels in a GHRH-treated subject did not increase by $\geq 15\%$, the amount of drug was doubled to $\sim 2$ mg in 1 ml of diluent. To maintain the blind, a placebo subject was also instructed to increase his/her injection “dose” in a yoked fashion. By the end of the study, 83 of the 89 subjects who completed the study were self-injecting the initial dose of 1 mg while 6 were self-injecting a 2 mg dose of drug or placebo. Subjects continued to inject either GHRH or placebo during their T2 stay in the GCRC.

On the second day of both the T1 and T2 assessments, subjects were administered a battery of cognitive tasks. The battery was designed to both cover a range of cognitive functions and to include cognitive functions both that have been shown to decline with advancing age (e.g., W AIS performance, single–dual task, finding as, verbal Sets) and those which have not (W AIS vocabulary, measures of verbal fluency).

The battery was divided into a morning and an afternoon session. Each subject was administered the same tests in the same order and at the same time during both assessments. A single psychometrist who was experienced in working with older adults administered the cognitive tests.

This cognitive assessment included the following tasks:

1. The Wechsler Adult Intelligence Scale—revised (WAIS-R)

All five of the W AIS performance scales; picture completion, picture arrangement, block design, object assembly and digit-symbol substitution, and one of the six W AIS verbal scales, vocabulary, were administered. Because the age of a number of study subjects exceeded 74, the upper limit for the age norms developed by Wechsler, raw scores were converted to scaled scores and a performance scale intelligence quotient (PIQ) using the Mayo W AIS-R age norms developed by Ivnik and colleagues.

2. The single–dual task (SDT)

Single–dual task is a computer-based task consisting of three components, the single task (ST), the dual task (DT) and a calculated dual task minus single task (DT−ST) score. The ST requires response to the position (right or left) of the stimuli, which consists of a pair of letters. The DT requires responding to position and saying whether the two letters were the same or different. Median reaction times for ST, DT and DT−ST were used for analysis. Note that SDT data were available for 79 subjects (37 GHRH, 39 Placebo), as this task was added to the battery sometime shortly after the study had started.

3. The finding A’s task (FINDA)

Finding A’s requires subjects to identify the five words containing the letter “A” in each of a series of columns of 41 words. The mean number correct across two trials was used for analysis.

4. The verbal sets task (LETSET)

Verbal Sets is computer-based task with two sets of two, three or four letters presented sequentially. One letter in each set is different. Subjects report out loud the letters that were unique to each set. The total correct score, summed across all three series and weighted by degree of difficulty of each trial was used for analysis.

5. The category fluency task (CATFLU)

CATFLU requires naming as many items as possible within 1 min in each of the following categories; animals, fruits and vegetables. The mean fluency score across the three categories was used for analysis.

6. The FAS verbal fluency task (FAS)

FAS requires naming as many words as possible beginning with the letters F, A and S. Mean fluency score across the three categories was used for analysis.

3. Results

Table 1 shows the size, gender and estrogen status composition of the two study groups. Sex, estrogen-status, age, education, mental status and level of depressive affect did not differ significantly between groups at baseline.

The GHRH dose was well tolerated; side effects were uncommon with some subjects occasionally reporting erythema or swelling at the injection site (~2% of subjects). Twenty-four hour mean GH increased by an average of 100% ($p < 0.001$) in the GHRH treated group. Similar significant increases were observed separately for men (79%, $p < 0.05$), women not on estrogen therapy (NET, 98%, $p < 0.05$), and women on estrogen therapy (ET, 121%, $p < 0.03$). No significant increases in GH were observed for the placebo group ($0\%$, n.s.). IGF-I increased 33.8% ($p < 0.001$) in the GHRH treated group. Similar significant increases were observed separately for men (32.4%, $p < 0.005$), women not on estrogen therapy (NET, 35.0%, $p < 0.05$), and women on estrogen therapy (ET, 35.1%, $p < 0.03$). No significant increases in IGF-I were observed for the placebo group (0.8%, n.s.).

Baseline (T1) and 6 months/treatment (T2) cognitive test scores of the GHRH and placebo groups are reported in Table 2. A $2 \times 2$, group $\times$ time ($G \times T$) ANOVA was con-

<p>| Table 1 |</p>
<table>
<thead>
<tr>
<th>Study participant characteristics</th>
<th>GHRH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (men/ET/NET)</td>
<td>44 (17/13/14)</td>
<td>45 (18/16/11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.32 (0.97)</td>
<td>67.69 (0.81)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.03 (0.46)</td>
<td>16.37 (0.57)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.39 (0.20)</td>
<td>28.31 (0.19)</td>
</tr>
<tr>
<td>CESD</td>
<td>4.16 (0.59)</td>
<td>3.56 (0.60)</td>
</tr>
</tbody>
</table>

* Means (standard error of the mean) for age, education, mini mental status exam (MMSE), and Center for Epidemiological Studies Depression (CESD) Scale and group sample sizes (N) and number of men, women on estrogen therapy (ET) and women not on estrogen therapy (NET) for growth hormone releasing hormone (GHRH) and Placebo groups are shown.
Table 2: Baseline (T1) and 6-month treatment (T2) cognitive test means for growth hormone releasing hormone and Placebo group

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>GHRH</th>
<th>Placebo</th>
<th>G x T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T1</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td></td>
<td>p</td>
</tr>
<tr>
<td>WAIS PIQ</td>
<td>114.68 (1.82)</td>
<td>119.02 (1.68)</td>
<td>115.22 (1.73)</td>
</tr>
<tr>
<td>WAIS picture completion</td>
<td>12.64 (0.47)</td>
<td>12.89 (0.42)</td>
<td>12.89 (0.41)</td>
</tr>
<tr>
<td>WAIS block design</td>
<td>12.07 (0.39)</td>
<td>13.36 (0.39)</td>
<td>12.82 (0.45)</td>
</tr>
<tr>
<td>WAIS object assembly</td>
<td>11.59 (0.44)</td>
<td>12.07 (0.44)</td>
<td>11.13 (0.41)</td>
</tr>
<tr>
<td>WAIS performance IQ</td>
<td>10.73 (0.35)</td>
<td>11.82 (0.39)</td>
<td>11.04 (0.42)</td>
</tr>
<tr>
<td>WAIS digit symbol</td>
<td>11.27 (0.43)</td>
<td>12.05 (0.39)</td>
<td>11.16 (0.42)</td>
</tr>
<tr>
<td>ST (ms)</td>
<td>455.74 (16.93)</td>
<td>451.44 (16.76)</td>
<td>458.72 (13.19)</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>731.00 (25.41)</td>
<td>714.33 (25.01)</td>
<td>720.83 (21.33)</td>
</tr>
<tr>
<td>DT − ST (ms)</td>
<td>277.36 (21.73)</td>
<td>262.89 (18.53)</td>
<td>262.09 (19.35)</td>
</tr>
<tr>
<td>FINDA</td>
<td>24.72 (0.91)</td>
<td>26.37 (0.99)</td>
<td>26.23 (0.79)</td>
</tr>
<tr>
<td>LETSET</td>
<td>55.90 (2.97)</td>
<td>58.33 (2.55)</td>
<td>57.86 (2.38)</td>
</tr>
<tr>
<td>CATFLLU</td>
<td>16.31 (0.81)</td>
<td>16.94 (0.77)</td>
<td>17.84 (0.55)</td>
</tr>
<tr>
<td>FAS</td>
<td>14.42 (0.63)</td>
<td>15.18 (0.61)</td>
<td>14.77 (0.54)</td>
</tr>
<tr>
<td>WAIS vocabulary</td>
<td>13.06 (0.42)</td>
<td>13.82 (0.40)</td>
<td>13.33 (0.55)</td>
</tr>
</tbody>
</table>

* Cognitive test results are reported for: WAIS performance IQ (PIQ); the five WAIS performance scales; the single (ST), dual–single (DT), and dual–dual (DT − ST) components of the single–dual task; the finding A’s task (FINDA); the letter set task (LETSET); the category fluency task (CATFLLU); the FAS task (FAS); and the WAIS vocabulary scale. Significance levels (two-tailed) for 2 × 2 components of the single–dual task; the finding A’s task (FINDA); the letter set task (LETSET); the category fluency task (CATFLLU); the FAS task (FAS); and the WAIS vocabulary scale. Significance levels (two-tailed) for 2 × 2 ANOVA group × time (T1 × T2) interactions are shown. N.B.: for ST, DT and DT − ST median (standard error of the mean) rather than mean scores are reported for a total of 76 subjects (37 GHRH, 39 Placebo). Significant T1 vs. T2 paired, post-hoc comparisons are indicated by.
† For GHRH (p < 0.03, 2-tailed).
* For Placebo (p < 0.05, 2-tailed).

To evaluate whether GHRH administration had comparable effects for subjects who were relatively more cognitively impaired, a new grouping variable was created to classify subjects as lower or higher functioning. Using a mini-mental status exam (MMSE) cut-point score of 27, each significant outcome variable was reanalyzed with a three-way (cognitive status, treatment condition, study visit) repeated measures ANOVA. Consistent with the results presented above, the results of all analyses supported significant treatment group × study visit interactions for subjects falling on either side of the MMSE cut-point. However, there was no evidence that the nature of this effect differed for lower and higher functioning subjects (three-way interaction for PA, PIQ, DT − ST, FINDA, LETSET, IGF-I, all p-values >0.7). That is, the effect of GHRH administration both on cognition and on IGF-I appear to be independent of cognitive level. This suggests that GHRH intervention could have a similar effect for a group of subjects with impaired cognitive function, such as those diagnosed with mild cognitive impairment.

4. Discussion

This study provides the first clear evidence that GHRH treatment, with its resultant increases in GH and IGF-I, improves the cognitive function of healthy older men and women. Overall, GHRH treatment was associated with improved performance on a number of cognitive tasks. Six months of GHRH treatment resulted in significant improvement (~6%) in cognitive functions, particularly those that involve problem solving and psychomotor processing speed.
of older individuals with impaired cognitive function, such as those with MCI or AD, is compelling, and its potential usefulness in enhancing cognitive function warrants thorough exploration.

5. Conflict of interest statement

Dr. Vitiello has served as a scientific consultant for Serono Laboratories Inc. Dr. Schwartz has served as a scientific consultant, given lectures supported by and received research support from Serono Laboratories Inc.

Acknowledgments

The authors wish to thank Drs. Laura D. Baker, Suzanne Craft and Beth Kerr for their collaboration. Dr. Peter P. Vitaliano for his methodological advice, and Suzanne Barsness, Gwen Drolet, Monika Kletke, Erin Madar and the nursing staff of the UWMC GCRC for their expert assistance in conducting this research. This research was supported by US Public Health Service grants K02-MH1158 (MVV), MH53575 (MVV), AG10943 (RSS) and the US Department of Veteran’s Affairs. A portion of this work was conducted through the General Clinical Research Center facility at the University of Washington Medical Center supported by the National Institutes of Health, Grant M01-RR-00037. GEREF® and placebo were provided free of cost by Serono Laboratories Inc. Contribution of the authors: Dr. Michael V. Vitiello, principal investigator, was responsible for all aspects of the current study and one of the parent studies (MH53575). Dr. Karen E. Moe, co-investigator, helped design and write one of the parent studies, helped design the cognitive test battery and participated in data analysis. Dr. George R. Merriam, co-investigator, responsible for the GH and IGF-I assays, subject safety and GHRH dosing. Dr. Giuliana Mazzoni, co-investigator, helped design the cognitive test battery. Dr. David H. Buchner, co-investigator, helped design and write the one of parent studies (AG10943). Dr. Robert S. Schwartz, co-investigator, was responsible for all aspects of one of the parent studies (AG10943).

References


