Growth hormone releasing hormone improves the cognition of healthy older adults

Michael V. Vitiello [a,*], Karen E. Moe [a], George R. Merriam [b,c],
Giuliana Mazzoni [d], David H. Buchner [e], Robert S. Schwartz [f]

[a] *Department of Psychiatry and Behavioral Sciences, BB-1520D Health Science Building, University of Washington,
Box 356560, 1959 NE Pacific Street, Seattle, WA 98195-6560, USA*
[b] *Department of Medicine, University of Washington and Veterans Affairs (VA) Puget Sound Health Care System, Seattle, WA USA*
[c] *University of Washington and Veterans Affairs (VA) Puget Sound Health Care System, Seattle, WA, USA*
[d] *Department of Psychology, Seton Hall University South Orange, NJ, USA*
[e] *Centers for Disease Control and Prevention, Atlanta, GA, USA*
[f] *Department of Medicine, University of Colorado Health Science Center Denver, CO, USA*

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).
© 2005 Elsevier Inc. All rights reserved.

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

* Corresponding author. Tel.: +1 206 6163444; fax: +1 206 6163319.
E-mail address: vitiello@u.washington.edu (M.V. Vitiello).

[6,7,19,20] 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 somatotrophic 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 somatotrophic axis can influence cognition, an obvious and important question that the current study seeks to answer is whether somatotrophic supplementation can improve cognitive function in healthy older adults. The current study employs GHRH rather than GH to augment the somatotrophic 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 somatotrophic 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 *Ginko 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 (two 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) NH_2 (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 ~ 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., WAIS performance, single–dual task, finding as, verbal Sets) and those which have not (WAIS 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 WAIS performance scales; picture completion, picture arrangement, block design, object assembly and digit-symbol substitution, and one of the six WAIS 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 WAIS-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 ($\sim 2\%$ 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 2×2, group $\times$ time ($G \times T$) ANOVA was con-

Table 1
Study participant characteristics[a]

	GHRH	Placebo
N (men/ET/NET)	44 (17/13/14)	45 (18/16/11)
Age (years)	68.32 (0.97)	67.69 (0.81)
Education (years)	16.03 (0.46)	16.37 (0.57)
MMSE	28.39 (0.20)	28.31 (0.19)
CESD	4.16 (0.59)	3.56 (0.60)

[a] 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[a]

Cognitive test	GHRH		Placebo		$G \times T$
	T1	T2	T1	T2	p
WAIS PIQ	114.68 (1.82)	119.02 (1.68)	115.22 (1.73)	116.60 (1.53)	0.02[†]
WAIS picture completion	12.64 (0.47)	12.89 (0.42)	12.89 (0.41)	12.69 (0.42)	
WAIS picture arrangement	12.07 (0.39)	13.36 (0.39)	12.82 (0.45)	12.76 (0.37)	0.01[†]
WAIS block design	11.59 (0.44)	12.07 (0.44)	11.13 (0.41)	11.31 (0.43)	
WAIS object assembly	10.73 (0.35)	11.82 (0.39)	11.04 (0.42)	11.73 (0.43)	
WAIS digit symbol	11.27 (0.43)	12.05 (0.39)	11.16 (0.42)	11.58 (0.37)	
ST (ms)	455.74 (16.93)	451.44 (16.76)	458.72 (13.19)	449.01 (12.30)	
DT (ms)	733.10 (25.41)	714.33 (25.01)	720.82 (22.13)	745.45 (22.29)	0.09[*]
DT − ST (ms)	277.36 (21.73)	262.89 (18.53)	262.09 (19.35)	296.43 (17.00)	0.03[*]
FINDA	24.72 (0.91)	26.37 (0.99)	26.23 (0.79)	26.21 (0.77)	0.03[†]
LETSET	55.90 (2.97)	59.33 (2.55)	57.56 (2.38)	56.68 (2.50)	0.07[†]
CATFLU	16.51 (0.68)	16.94 (0.77)	17.84 (0.58)	17.87 (0.59)	
FAS	14.42 (0.63)	15.18 (0.61)	14.77 (0.54)	15.26 (0.63)	
WAIS vocabulary	13.00 (0.42)	13.82 (0.40)	13.33 (0.55)	13.40 (0.46)	

[a] Cognitive test results are reported for: WAIS performance IQ (PIQ); the five WAIS performance scales; the single (ST), dual (DT) and dual–single (DT − ST) components of the single–dual task; the finding A's task (FINDA); the letter set task (LETSET); the category fluency task (CATFLU); the FAS task (FAS); and the WAIS vocabulary scale. Significance levels (two-tailed) for 2×2 ANOVA group × time ($G \times T$) 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 ($p < 0.01$, 2-tailed).

[*] For Placebo ($p < 0.05$, 2-tailed).

ducted for each of the cognitive tasks with age and years of education as co-variates. Significant (2-tailed) $G \times T$ interactions or non-significant trends were observed for WAIS performance IQ (PIQ, $p < 0.02$), WAIS picture arrangement (WAIS PA, $p < 0.01$), the dual task (DT, $p < 0.09$), the dual task minus single task (DT − ST, $p < 0.03$), the finding A's task (FINDA, $p < 0.03$) and the letter series task (LETSET, $p < 0.07$). Paired, T1 versus T2, post-hoc comparisons revealed significant (2-tailed) increases in WAIS PIQ ($p < 0.01$), WAIS PA ($p < 0.01$), FINDA ($p < 0.01$), and LETSET ($p < 0.01$) scores for the GHRH group. Significant ($p < 0.05$) increases in DT and DT − ST, indicating slowed processing speed, were observed in the placebo group, but not in the GHRH group, which actually demonstrated non-significant improvements (decreases) in processing speed on both of these measures. No changes were observed in any of the other tasks for either GHRH or placebo group.

Correlational analyses relating plasma GH and IGF-I levels to cognitive outcome measures indicated that for the GHRH-treated group, higher 24 h mean GH levels at T2 (month 6) were associated with higher WAIS-R digit-symbol subtest scores ($r = 0.49$, $p < 0.001$) and higher WAIS-R Performance IQ scores overall ($r = 0.40$, $p = 0.01$). For IGF-1, greater increases in plasma level associated with GHRH administration at T2 relative to T1 were associated with higher scores on the FAS verbal fluency test ($r = 0.41$, $p = 0.006$).

The GHRH effect on cognition was also examined separately for men, and for women as a function of estrogen status (see the breakdown of men, women on estrogen (ET) and women not on estrogen (NET) in Table 1). It was found that neither gender, nor estrogen status interacted with the observed GHRH effect on cognition.

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

(e.g., WAIS-R PIQ, WAIS-R PA, SDT, FINDA) and working memory (LETSET) of both healthy older men and women.

The pattern of findings in the SDT task revealed that GHRH had no impact on motor reaction time per se, measured by the ST component of the task, but rather impacted cognitive processing speed (measured by the DT and DT minus ST components of the task). It is of particular interest that novel problem solving, cognitive processing speed and working memory all showed improvement with GHRH treatment, as these are three areas of cognitive function that demonstrate well documented age-related deficits. Conversely the three cognitive tasks that showed no change with GHRH treatment, CATFLU, FAS and WAIS-R vocabulary, represent the highly over-learned verbal knowledge, often called "crystallized intelligence", that is, relatively well preserved with age. A lack of any observed GHRH mediated changes here may well be a "ceiling effect".

At this time it is unclear whether the observed effects are the result of increased microvascularity and related changes in cerebral blood flow per se, the direct paracrine actions of IGF-I (e.g., via NMDA receptors) or both [12,13]. However, given the density of type 1 IGF-I receptors in cortical areas supporting abilities such as declarative memory, it is conceivable that IGF-I supplementation via GHRH administration is a likely mechanism for this study's observed facilitatory effects on cognitive function.

The positive effects of GHRH on cognitive function were unaffected either by gender or by the estrogen status of the women who participated in the study. Further there was no evidence to indicate that the effect of GHRH treatment was moderated by cognitive capacity, suggesting that GHRH may also improve cognitive function in those populations for whom cognitive function may be impaired, e.g., mild cognitive impairment (MCI) or Alzheimer's disease (AD) patients.

When provocative and potentially clinically useful findings such as these are reported, the question often arises as to whether or not they are "clinically meaningful". Defining what a "clinically meaningful" change is in terms of improving cognitive function is problematic at best and certainly not at all straightforward. For example, is a five-point rise in WAIS PIQ, as was observed here following GHRH treatment, clinically meaningful? It might well be argued that anyone offered such an opportunity to increase in their cognitive capacities is not likely to refuse such an offer, provided the costs and side-effects are not inordinate or excessive. Certainly the power and the effect sizes of the changes in cognition observed in the current study (0.44–0.61 and 0.19–0.37, respectively) are of moderate magnitudes, which suggest that they may well have practical, as well as statistical, significance. Whether or not such changes prove to be ultimately "clinically meaningful" will depend on the outcome of future research in this area.

Certainly the rationale for further study of GHRH effects on cognition in healthy older adults generally and particularly 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

Acknowledgments

References

[1] Adem A, Jossan SS, d'Argy R, Gillberg PG, Nordberg A, Winblad B, et al. Insulin-like growth factor 1 (IGF-I) receptors in the human brain: quantitative autoradiographic localization. Brain Res 1989;503:299–303.

[2] Aleman A, Verhaar HJ, de Haan EHF, De Vries WR, Samson MM, Drent ML, et al. Insulin-like growth factor-I and cognitive function in healthy older men. J Clin Endocrinol Metab 1999;84:471–5.

[3] Baum HB, Katznelson L, Sherman JC, Biller BM, Hayden DL, Schoenfeld DA, et al. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. J Clin Endocrinol Metab 1998;83(9):3184–9.

[4] Connor B, Beilharz EJ, Williams C, Synek B, Gluckman PD, Faull RL, et al. Insulin-like growth factor-I (IGF-I) immunoreactivity in the

Alzheimer's disease temporal cortex and hippocampus. Mol Brain Res 1997;49:283–90.

[5] Connor B, Dragunow M. The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Res Rev 1998;27:1–39.

[6] Deijen JB, de Boer H, Blok GJ, van der Veen EA. Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 1996;21:313–22.

[7] Deijen JB, de Boer H, van der Veen EA. Cognitive changes during growth hormone replacement in adult men. Psychoneuroendocrinology 1998;23(1):45–55.

[8] Johansson JO, Larson G, Andersson M, Elmgren A, Hynsjo L, Lindahl A, et al. Treatment of growth hormone-deficient adults with recombinant human growth hormone increases concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters. Neuroendocrinology 1995;61:57–66.

[9] Lackey BR, Gray SL, Henricks DM. Actions and interactions of the IGF system in Alzheimer's Disease: review and hypotheses. Growth Horm IGF Res 2000;10:1–13.

[10] Lai Z, Roos P, Zhai O, Olsson Y, Fholenhag K, Larsson C, et al. Age-related reduction of human growth hormone-binding sites in the human brain. Brain Res 1993;621:260–6.

[11] Lichtenwalner RJ, Forbes ME, Bennett SA, Lynch CD, Sonntag WE, Riddle DR. Intercerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience 2001;107(4):603–13.

[12] Lynch C, Lyons D, Khan A, Bennett SA, Sonntag WE. Insulin-like growth factor-I selectively increases glucose utilization in brains of aged animals. Endocrinology 2001;142(1):506–9.

[13] Merriam GR, Schwartz RS, Vitiello MV. Growth hormone-releasing hormone and growth hormone secretagogues in normal aging. Endocrine 2000;22:41–8.

[14] Nyberg F, Burman P. Growth hormone and its receptors in the central nervous system: location and functional significance. Horm Res 1996;45:18–22.

[15] Nyberg F. Aging effects on growth hormone receptor binding in the brain. Exp Gerontol 1997;32:521–8.

[16] Papadakis M, Grady D, Tierney M, Black D, Wells L, Grunfeld C. Insulin-like growth factor I and functional status in healthy older men. J Am Geriatr Soc 1995;43(12):1350–5.

[17] Rollero A, Murialdo G, Fonzi S, Garrone S, Gianelli MV, Gazzerro E, et al. Relationship between cognitive function, growth hormone and insulin-like growth factor I plasma levels in aged subjects. Neuropsychobiology 1998;23:45–55.

[18] Soares CD, Musolino NR, Cunha Neto M, et al. Impact of recombinant human growth hormone (rhGH) treatment on psychiatric, neuropsychological and clinical profiles of GH deficient adults. A placebo-controlled trial. Arq Neuropsiquiatr 1999;57(2A):182–9.

[19] Sartorio A, Conti A, Molinari E, Riva G, Morabito F, Faglia G. Growth, growth hormone and cognitive functions. Horm Res 1996;45:23–9.

[20] Sartorio A, Molinari E, Riva G, Conti A, Morabito F, Faglia G. Growth hormone treatment in adults with childhood onset growth hormone deficiency: effects on psychological capabilities. Horm Res 1995;44(1):6–11.

[21] Sonntag W, Brunso-Bechtold J, Riddle D. Age-related decreases in growth hormone and insulin-like growth factor (IGF)-I: implications for brain aging. J Anti-Aging Med 2001;4(4):311–30.

[22] Sonntag W, Lynch C, Thornton P, Khan A, Bennett S, Ingram R. The effects of growth hormone and IGF-1 deficiency on cerebrovascular and brain ageing. J Anat 2000;197(Pt 4):575–85.

[23] Sonntag W, Lynch C, Cooney P, Hutchins P. Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1. Endocrinology 1997;138(8):3515–20.

[24] Thornton P, Ingram R, Sonntag W. Chronic [D-Ala 2]-growth hormone-releasing hormone administration attenuates age-related deficits in spatial memory. J Gerontol A Biol Sci Med Sci 2000;55(2):B106–12.

[25] Thornton P, Ng A, Sonntag W. Insulin-like growth factor-1 modulates learning and memory in young and old rats. Soc Neurosci Abstr 1999;25:1064.

[26] van Dam PS, Aleman A, de Vries WR, Deijen JB, van der Veen EA, de Haan EH, et al. Growth hormone, insulin-like growth factor I and cognitive function in adults. Growth Horm IGF Res 2000;(Suppl. B):69–73.

[27] Van der Reijden-Lakeman IE, de Sonneville LM, Swaab-Barneveld HJ, Slijper FM, Verhulst FC. Evaluation of attention before and after 2 years of growth hormone treatment in intrauterine growth retarded children. J Clin Exp Neuropsychol 1997;19(1):101–18.

[28] Vitiello MV, Merriam GR, Moe KE, Drolet G, Barsness S, Klelte M, et al. IGF-I correlates with cognitive function in healthy older men and estrogenized women. Gerontologist 1999;39(Special Issue 1):6.