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Insulin-Like Growth Factor-I and Cognitive Function in Healthy Older Men

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ABSTRACT

The GH/insulin-like growth factor-I (GH/IGF-I) axis is known to be involved in aging of physiological functions. Recent studies indicate that the GH/IGF-I axis may be associated with cognitive functioning. The aim of the present study was to determine whether the age-related decline in circulating levels of IGF-I, as an index of anabolic status, is associated with cognitive functions that are known to decline with aging, but not with cognitive functions not sensitive to aging.

Twenty five healthy older men with well-preserved functional ability participated in the study. We also administered neuropsychological tests of general knowledge, vocabulary, basic visual perception, reading ability, visuoconstructive ability, perceptual-motor speed, mental tracking, and verbal long-term memory. Performance on the last four tests decline with aging, whereas the first four of these tests have been shown not to be sensitive to cognitive aging. Mean age of the subjects was 69.1 ± 3.4 (SD) yr (range 65–76 yr), their mean body mass index was 27.0 ± 2.4 kg/m^2, and their mean IGF-I level was 122 ng/mL (range: 50–220). We found IGF-I levels to be significantly associated with the performances (controlled for education) on the Digit Symbol Substitution test ($r = 0.52$, $P = 0.009$) and the Concept Shifting Task ($r = -0.55$, $P = 0.005$), which measure perceptual-motor and mental processing speed. Subjects with higher IGF-I levels performed better on these tests, performance on which is known to decline with aging.

In conclusion, the results of this study support the hypothesis that circulating IGF-I may play a role in the age-related reduction of certain cognitive functions, specifically speed of information processing. (*J Clin Endocrinol Metab* **84**:471–475, 1999)

THE ACTIVITY of the GH/insulin-like growth factor-I (IGF-I) axis declines significantly with aging (1). Both aging and GH deficiency are associated with reduced lean body mass, reduced protein synthesis, increased adiposity, and decreased bone mass. Hoffman *et al.* (2) termed this syndrome the somatopause, in older individuals. Several investigators studied the effects of GH replacement on body composition in healthy older adults. These studies showed increased lean body mass and decreased adipose tissue mass after administration of GH (3–5). GH may also affect cognitive and emotional functioning (see Ref. 6 for a review). For example, significant cognitive deficits have been reported in GH-deficient (GHD) children (7, 8). Furthermore, impaired psychosocial functioning and personality development have been documented in GHD children (9, 10). In GHD adults, neuropsychological deficits have also been observed (6, 11, 12). For example, Deijen *et al.* (11) demonstrated subnormal memory performance in GHD adults. Zelissen *et al.* (12) conducted a profile analysis on the results of a number of neuropsychological tests administered to GHD adults. They report deficits in memory retrieval of verbal information, compared with the normal (Dutch) range.

In the light of these findings, the hypothesis may be considered that GH is not only involved in aging of physiological functions (1), but is also associated with the gradual decline of specific cognitive functions in aging. Age-related decline in cognitive functions has been extensively documented in several domains (13–16). For example, performance on tests of explicit memory retrieval declines significantly during the process of aging (17). In describing preserved and impaired functions, a major distinction was proposed by Catell (18), between fluid and crystallized intelligence. Specifically, the group of abilities usually referred to as fluid intelligence is found to be relatively vulnerable to the effects of aging (16, 19). These abilities include nonverbal reasoning, planning of behavior, rule discovery, and concept formation. In contrast, crystallized intelligence does not markedly decline with increasing age (19). Crystallized intelligence refers to abilities dependent upon the accumulation of all sorts of educational experiences during a lifetime, and includes formal verbal reasoning, comprehension of culture-specific rules and strategies, and general fund of knowledge. Recently, in explaining age-related differences in measures of fluid cognition, theories of cognitive aging focus on the speed with which many processing operations can be executed. Reduction of mental processing speed is thought to contribute significantly to the age-related cognitive decline (20, 21).

The stimulating action of GH on growth and differentiation of various tissues is mediated by IGF-I. Because GH is secreted in a pulsatile manner, IGF-I is a more convenient marker of GH secretion (22). Although a strong positive

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relationship has been documented between serum IGF-I levels and spontaneous 24-h GH secretion in young adults (23), this relationship may be less in older subjects (23, 24), although recently Vermeulen *et al.* (25) reported a close relationship between the age-related decline in mean plasma 24-h GH levels and IGF-I levels. IGF-I exerts its anabolic effects also independently of GH, and is considered to be an index of anabolic status.

The aim of the present study was to investigate in healthy older male subjects the association between serum IGF-I levels and cognitive functions sensitive and not sensitive to aging. An association between IGF-I levels and cognitive functions sensitive to aging would support the hypothesis that age-related changes in the activity of the GH/IGF-I axis contribute to cognitive decline with aging.

Subjects and Methods

Subjects

Subjects were retrieved from a database of volunteers from the Department of Geriatrics and Bone Metabolism of the University Hospital Utrecht (volunteers for this database were recruited by advertisement in a local newspaper). Twenty five male subjects [age: 69.1 ± 3.4 yr, (mean ± SD); body mass index: 27.0 ± 2.4 kg/m^2; body fat mass: 23.7 ± 6.8%; waist/hip ratio: 1.06 ± 0.06] participated in the study. Informed consent was obtained from all subjects. The study was approved by the Ethics Committee at the University Hospital Utrecht. Education was coded as the number of years of education. Because health-related factors may contribute significantly to cognitive decline (26, 27), all subjects were carefully screened by physical examination and a health questionnaire (28). Only healthy ambulatory subjects without specific disorders and/or medication were included.

Testing procedure

Subjects were tested individually in a quiet room. The sequence in which tests were administered was identical for all subjects. The testing procedure took about 2 h. Subjects were tested in the morning, after blood samples were obtained.

For all subjects, neuropsychological tests were carried out by the same author (A.A.), who was not aware of the IGF-I levels.

Neuropsychological tests

To investigate whether the age-related decline in GH secretion may be associated with the neuropsychological profile characteristic of cognitive aging, tests sensitive to aging (so-called Don't Hold tests) were administered, along with tests not sensitive to aging (Hold tests). Salthouse (15) and La Rue (16) provide an overview of neuropsychological tests used in aging research. Table 1 lists the tests we selected for the present study, and a short description of each test is given below. Only tests with high reliability and validity were included (a detailed review of psychometric properties can be found in Refs. 29 and 30 and references cited in Table 1).

Information. A subtest from the Wechsler Adult Intelligence Scale (WAIS) that covers general knowledge. It consists of 32 questions of increasing difficulty. Hence, persons with little schooling do not perform as well as those with more schooling.

Vocabulary. A WAIS subtest of verbal ability that correlates highly with level of education. The subject is asked to define 35 vocabulary words of increasing difficulty.

Benton Judgement of Line Orientation. This test measures basic perceptual processes contributing to extrapersonal spatial perception. The test requires the subject to identify which 2 of 11 lines presented in a semicircular array have the same orientation in two-dimensional space as two target lines.

Brus Reading test. A test of reading speed. Subjects are required to read a list of words. The number of words correctly pronounced within 1 min is recorded.

Block Design. A WAIS subtest that measures perceptual organization and construction. Subjects are asked to construct a visual-spatial pattern with colored blocks.

Digit Symbol Substitution. Also a WAIS subtest, it measures cognitive and perceptual-motor processing speed. The subject is given a code that pairs symbols with digits. The test consists of matching as many series of digits to their corresponding symbols as possible in 90 sec.

Concept Shifting Task. A test of planning of movement, visuomotor tracking, and processing speed. The subject has to mark numbers and letters as fast as possible in a specific sequence: 1-A-2-B etc. The numbers and letters are randomly distributed in a circle. In a control condition, empty circles have to be marked in a clockwise fashion. When subtracting this condition from the experimental condition, it is possible to control for (peripheral) motor speed.

15-Word test. The Dutch version of the Rey Auditory Verbal Learning Task is a test for long-term memory retention. Fifteen words are read to the subject, who is required to report as many words as he can remember immediately after presentation. After a delay of 15 min (in which another test, the Judgement of Line Orientation, is administered), the subject is asked to recall as many words as possible from memory.

Hormone assays

Venous blood samples were drawn in the morning after an overnight fast. The samples were immediately centrifuged (6000 rpm, 20 min, 4 C) and stored at −20 C until final analysis. Aliquots of sera of 1 mL, acidified by addition of 1 mL 0.5 M HCl, containing 5 mM $CaCl_2$ were incubated at room temperature for 1 h. Subsequently, IGFs were separated from IGF binding proteins by Sep-Pak C18 cartridge chromatography (31). IGF-I levels were determined in duplicate by a commercially available RIA, using the antiserum from Underwood and van Wijk, distributed by the NIDDK (32). The minimum detectable concentration was 20 ng/mL. At a concentration of 200 ng/mL, the intraassay coefficient of variation (CV) was 7.9%, and the in-between CV was 5.9%.

TABLE 1. Neuropsychological tests used in study

Neuropsychological test	Function measured	Reference
Hold		
Information (WAIS)	General knowledge	51
Vocabulary (WAIS)	Verbal ability, vocabulary	51
Benton Line Orientation	Basic visuospatial perception	52
Brus Reading test	Reading ability, reading speed	53
Don't hold		
Block Design (WAIS)	Perceptual organization and construction	51
Digit Symbol Substitution (WAIS)	Cognitive and perceptual-motor processing speed	51
Concept Shifting Task	Planning of movement, cognitive processing speed	54
15-Word test	Verbal long-term memory	29

Statistical analysis

Pearson's correlation coefficients (r) are used to describe the association between variables. To determine the relationship between IGF-I levels and measures of cognitive function, partial correlation coefficients were computed. The accepted level of significance was set at $P < 0.01$ (two-tailed). We controlled for education, because previous research has shown that the level of education significantly affects neuropsychological task performance (27, 29). All statistical analyses were performed with the SPSS PC program (version 6.1.4; SPSS, Inc., Chicago, IL).

Results

The mean serum IGF-I level was 122 ng/mL, range 50–220, which is in the normal range for subjects of about 70 yr of age (33). The partial correlation between age and IGF-I levels was −0.40 ($P = 0.05$). The number of years of education was 14.7 ± 3.0 (mean ± SD). The partial correlation between education and IGF-I levels was not significant, $r = -0.06$, $P > 0.20$.

Highly significant correlations were noted between level of education and performances on Information ($r = 0.63$, $P = 0.001$), Vocabulary ($r = 0.69$, $P = 0.001$), Concept Shifting Task ($r = -0.54$, $P = 0.006$), Digit Symbol Substitution ($r = 0.61$, $P = 0.002$), and Block Design ($r = 0.54$, $P = 0.008$) tests. In contrast, the Brus Reading test, the 15-Word test, and the Benton Judgement of Line Orientation test showed no significant effect of education ($r = 0.28$, $P = 0.19$, $r = -0.01$, $P = 0.96$, and $r = -0.05$, $P = 0.81$, respectively). No association was observed between age and neuropsychological test performances ($P > 0.05$).

The partial correlation coefficients for IGF-I and the neuropsychological tests (controlled for level of education) are shown in Table 2. Significant associations between IGF-I levels and performance on the Digit Symbol Substitution test ($r = 0.52$, $P = 0.009$) and the Concept Shifting Task ($r = -0.55$, $P = 0.005$) were found (see Fig. 1). These tests are measures of perceptual-motor and mental processing speed. The correlation with Concept Shifting Task ($r = -0.55$) is negative, because scores are noted in seconds, with shorter times implying better performance, and is calculated after correction for motor speed by subtracting the control task. Without this subtraction the partial correlation was −0.59, $P = 0.002$. No significant correlations were obtained for the 15-Word test (long-term memory performance) and Block Design (visuoconstructive ability), as well as for the so-called Hold tests. Additional analyses, in which test performances were corrected both for age and education, yielded comparable results with those corrected for education alone: significant correlations between IGF-I *vs.* the Digit Symbol Substitution test ($r = 0.47$, $P < 0.01$) and *vs.* the Concept Shifting Task ($r = -0.47$, $P < 0.01$), and no associations with the other test performances.

TABLE 2. Partial correlations[a] between serum IGF-1 levels and cognitive test performance

	IGF-I	P value[b]
Hold		
Information	−0.16	0.47
Vocabulary	0.11	0.60
Brus Reading	0.31	0.14
Benton Line Orientation	−0.07	0.74
Don't hold		
Digit Symbol Substitution	0.52	0.009
Block Design	0.03	0.90
Concept Shifting[c]	−0.55	0.005
15-Word test (delayed recall)	−0.22	0.29

[a] Education entered as control variable.
[b] Two-tailed.
[c] Scores corrected for motor speed by subtracting control task.

Discussion

The present study was designed to examine the association of IGF-I levels with cognitive function in healthy older men. Therefore, we investigated whether the association between IGF-I and cognitive functions would be stronger for functions that decline with aging than for functions that do not decline with aging. After adjusting the performances of the neuropsychological tests for level of education, IGF-I levels were found to be significantly associated with better performances on two tests sensitive to the effects of aging, which both are measures of cognitive and perceptual-motor speed. This finding indicates that the activity of the GH/IGF-I axis may contribute to the age-related decline of certain cognitive functions. Specifically, in healthy older male subjects who are known to have a relatively wide range of IGF-I levels, IGF-I appears to affect mental processing speed and executive processing.

In light of recent theories of cognitive aging, the association between circulating IGF-I and processing speed is very interesting. For example, Salthouse (20) proposed that the reduction with increased age in the speed with which many cognitive operations can be executed is a major factor contributing to age-related differences in cognitive functioning. An increasing number of studies confirm that a large proportion of age-related variance in cognitive performance is shared with measures of the speed with which simple cognitive operations can be executed (21, 34). The relevant speed appears to be not merely related to the time required for motor processes such as manual movement, but is mainly related to the rate at which cognitive operations can be executed in the brain. Therefore, the reduction in speed with aging is not only peripheral but also central.

The association between IGF-I and measures of processing speed found in the present study is consistent with earlier findings by Papadakis *et al.* (33). In a study of 104 healthy elderly men (mean age 75 yr) they found a significant association between IGF-I levels and performance on the Digit Symbol Substitution. However, Papadakis *et al.* (33) found no significant association between IGF-I and the Trails B test, a speeded test of executive function very similar to the Concept Shifting Task in our present study, which is in contrast with our findings. It is important to note, however, that Papadakis *et al.* did not control for level of education, which is a major drawback of their study. Level of education of subjects is an important predictor of cognitive test performance (27).

Our results, which may suggest a role of GH in the age-related decline of mental processing speed are also in accordance with studies of GH replacement in healthy elderly subjects, as well as in GHD adults. In a 6-month GH substitution study in healthy older men (mean age 75 yr), Papadakis *et al.* (5) found improvement in body composition but not in functional abilities as muscle strength, physical

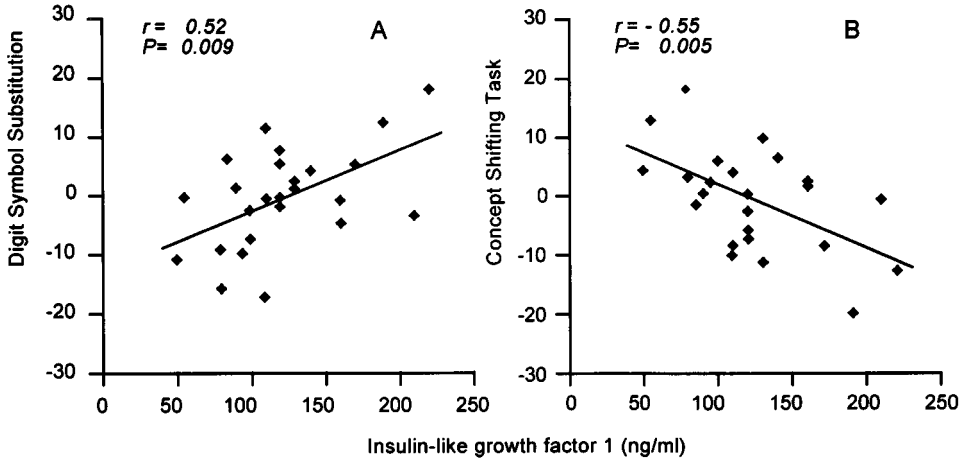

FIG. 1. Digit Symbol Substitution scores (A) and Concept Shifting Task scores (B) as a function of IGF-I (nanograms per milliliter) in 25 healthy older men. Both test scores are corrected for level of education.

performance, and systemic endurance. They also assessed the effects of GH replacement on cognitive function (Digit Symbol test, Trails B, and the Mini-Mental Status Examination). Papadakis *et al.* (5) report significant effects of GH treatment on the trails B score, but not on Digit Symbol or Mini-Mental Status Examination scores. Sartorio *et al.* (35) analyzed psychological performance in a group of adults with childhood onset GHD, before and after 6 months of recombinant GH therapy. After treatment, an overall improvement was reported on intellectual tasks, although it reached statistical significance only for the Digit Symbol substitution of the WAIS. Thus, the results of this study also point towards a possible role of GH in mental processing speed. In similar vein, a recent study reports a beneficial effect of GH treatment on attentional capacity in intrauterine growth retarded children, as measured with speeded psychological measures (36).

The lack of an association between IGF-I and memory performance in the present study was not expected, because memory performance has been shown to be affected in GHD adults (11) and GH substitution may improve memory performance in these subjects (37). However, it must be noted that we investigated healthy older subjects. It could well be that only strong reductions in circulating IGF-I, beyond a certain threshold, may be associated with significant decline in memory performance. The failure to observe significant relationships between age *vs.* IGF-I levels, respectively, *vs.* performances on Don't Hold tests, may be explained by the fact that we studied a group of subjects with a rather limited age range from 65–76 yr.

The exact mechanism behind the association between the activity of the GH/IGF-I axis and measures of cognitive functioning sensitive to aging is not known.

The action of GH in the central nervous system may occur by different mechanisms (38). First, GH may act directly on specific neural structures in the brain. This requires transport of GH over the blood-brain barrier (BBB). Indeed, several recent studies support the hypothesis that GH may pass the BBB (39, 40). In addition, the existence of GH binding sites has been reported in such brain areas as the hippocampus, hypothalamus, putamen, and choroid plexus (41). The number of GH binding sites in these areas decreases significantly with aging (41). The hippocampus is an important brain structure that plays an essential role in multiple cognitive processes, especially learning and memory (42). The age-related reduction of GH receptors in the hippocampus may contribute to subsequent decline in cognitive function. As a second potential mechanism, GH may release secondary mediators from peripheral tissues that pass the BBB and subsequently affect brain function. A known example of such a mediator is IGF-I. This mechanism may account for the effect of GH on cognitive function, because IGF-I receptors are widely distributed in the brain (43, 44) and evidence suggests that IGF-I plays a physiological role as a local neuroregulator and brain growth factor (45).

Recent findings on the effects of GH treatment on cerebrospinal concentrations of neurotransmitter metabolites suggest that GH affects brain neurotransmitter activity. For example, GH replacement has been found to reduce the concentrations of vasointestinal peptide, noradrenaline, and homovanillic acid, a dopamine metabolite (37, 46, 47). Dopamine is known to be involved in attentional function (48) and executive functions of the prefrontal cortex (49).

In this study, we examined only healthy ambulatory older men, who were living independently in the community. The results may therefore not be generalizable to older women or to infirmed older men. Another aspect may be the practical consequences of this study. What sort of studies are needed to learn whether administration of IGF-I improves or preserves cognitive functioning? Specifically, questions related to dosage, safety, and tolerance need to be answered before replacement therapy can be used in elderly subjects. Furthermore, potent (orally active) GH secretagogues have recently been developed (50), which may give further insight into causal links between the activity of the GH/IGF-I axis and age-sensitive cognitive functioning. Finally, reliable clinical endpoints for improvements in cognitive functioning should be developed to get insight into the risk/benefit ratio.

We conclude that serum IGF-I levels in healthy older male subjects are associated with better performance on tests of mental processing speed, which is known to decline significantly with aging. This finding suggests that the GH/IGF-I axis may play a role in the age-related decline of certain cognitive functions.

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