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 administered to GHD adults. They 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, reasoning, comprehension of culture-specific rules and strategies. 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).

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)
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/m²; 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). Salt-house (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).

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Function measured</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold</td>
<td>General knowledge</td>
<td>51</td>
</tr>
<tr>
<td>Information (WAIS)</td>
<td>Verbal ability, vocabulary</td>
<td>51</td>
</tr>
<tr>
<td>Vocabulary (WAIS)</td>
<td>Basic visuospatial perception</td>
<td>52</td>
</tr>
<tr>
<td>Benton Line Orientation</td>
<td>Reading ability, reading speed</td>
<td>53</td>
</tr>
<tr>
<td>Brus Reading test</td>
<td>Perceptual organization and construction</td>
<td>51</td>
</tr>
<tr>
<td>Don’t hold</td>
<td>Cognitive and perceptual-motor processing speed</td>
<td>51</td>
</tr>
<tr>
<td>Block Design (WAIS)</td>
<td>Planning of movement, cognitive processing speed</td>
<td>54</td>
</tr>
<tr>
<td>Digit Symbol Substitution (WAIS)</td>
<td>Verbal long-term memory</td>
<td>29</td>
</tr>
</tbody>
</table>

TABLE 1. Neuropsychological tests used in study

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 CaCl₂, 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%.
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 \( r = -0.40 \) (\( P = 0.05 \)). 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 task 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.

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

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**TABLE 2.** Partial correlations \(^a\) between serum IGF-I levels and cognitive test performance

<table>
<thead>
<tr>
<th></th>
<th>IGF-I</th>
<th>P value (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>–0.16</td>
<td>0.47</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>0.11</td>
<td>0.60</td>
</tr>
<tr>
<td>Brus Reading</td>
<td>0.31</td>
<td>0.14</td>
</tr>
<tr>
<td>Benton Line Orientation</td>
<td>–0.07</td>
<td>0.74</td>
</tr>
<tr>
<td>Don’t hold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Symbol Substitution</td>
<td>0.52</td>
<td>0.009</td>
</tr>
<tr>
<td>Block Design</td>
<td>0.03</td>
<td>0.90</td>
</tr>
<tr>
<td>Concept Shifting (^c)</td>
<td>–0.55</td>
<td>0.005</td>
</tr>
<tr>
<td>15-Word test (delayed recall)</td>
<td>–0.22</td>
<td>0.29</td>
</tr>
</tbody>
</table>

\(^a\) Education entered as control variable.  
\(^b\) Two-tailed.  
\(^c\) Scores corrected for motor speed by subtracting control task.
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). A potential mechanism is that IGF-I plays a role 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 exact mechanism behind the association between the activity of the GH/IGF-I axis and measures of cognitive function, sensitive to aging is not known. The mechanism 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).

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