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The relation between insulin-like growth factor I levels and cognition in healthy elderly: A meta-analysis

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Abstract

Objective: Insulin-like growth factor I (IGF-I) levels and cognitive functioning decrease with aging. Several studies report positive correlations between IGF-I levels and cognitive functioning in healthy elderly. However, because of controversial data no definitive conclusions can be drawn concerning the relation between IGF-I and cognition. Therefore, we carried out a meta-analysis on studies that report on the relation between IGF-I and cognition in healthy elderly.
Design: We searched the electronic databases for articles about IGF-I and cognition. Studies from 1985 to January 2005 are included. Two reviewers independently extracted data on study design and cognitive outcomes. Thirteen studies on IGF-I and cognition in elderly, with a total number of 1981 subjects, met the inclusion criteria. On the data from these studies meta-analyses were carried out by means of the program *Comprehensive Meta-analysis* using a random effects model.
Results: Pooled effects show that IGF-I levels in healthy elderly have a positive correlation with cognitive functioning, which appeared to be mainly measured with the mini mental state examination (MMSE). The effect size is 0.6, which indicates the presence of a large positive relationship between IGF and cognition in healthy elderly.
Conclusion: These meta-analyses showed an overall relationship between IGF-I levels and cognitive functioning in healthy elderly. Further studies should be performed to clarify the role of IGF-I substitution in preserving cognitive functions with aging.

Keywords: IGF-I; Cognition; Memory; Correlation; Elderly

1. Introduction

Decreased functioning of the growth hormone (GH)–insulin-like factor I (IGF-I) axis is found in patients with growth hormone deficiency (GHD) and in normal aging. Symptoms of GHD in adults are altered body composition, reduced bone mineral density and decreased cognitive functioning [1]. Features of aging resemble those of GHD, suggesting that the decreased circulating IGF-I level may play a role in age-related cognitive decline. The term "somatopause" points to the age-related changes in body composition, function and metabolism. These changes are mainly dependent on age-related variations in the hypothalamic control of the somatotropic function.

Both GH and IGF-I levels are found to be associated with cognitive functioning and quality of life (QoL) in several studies [2–4]. However, a recent meta-analysis on the relation between GH and QoL in patients with GHD showed no convincing evidence that GH substitution improves QoL [5]. The available data in the meta-analysis on cognitive functioning and GH was too limited to draw far reaching conclusions with respect to the impact of GH treatment on cognition in patients with GHD.

The exact mechanism of the relation between the GH–IGF-I axis and cognitive functioning is not known yet. Regarding the activity of GH–IGF-I on the brain,

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there is evidence that GH can cross the blood–brain barrier [6] and binding sites for GH and IGF-I are found in the brain in the choroid plexus, hypothalamus, putamen, thalamus and hippocampus [7,8]. In these brain areas, which play a role in mood and memory, the number of GH receptors declines with aging [9]. In addition, IGF potentiates acetylcholine release from the hippocampus and aging is associated with a dramatic reduction of IGF-I protein levels and receptor density in this structure [10,11]. Further, it has been found that GH significantly affects neural cell metabolism in adult men in studies showing changes in cerebrospinal fluid concentration of the dopamine metabolite homovanillic acid following GH treatment [6,12,13]. High levels of dopamine are found in the hippocampus, a structure that plays an important role in learning and memory. A change in the availability of GH in the hippocampus may alter the dopamine turnover in this area and influence memory processes [14].

GH and IGF-I have important functions in the development and differentiation of the central nervous system [15]. Growth and development of neurons in the dentate gyrus of the hippocampus are modulated by IGF. With aging reductions in IGF levels and in neurogenesis are shown. The molecular endocrinology and pathofysiologic effects of aging on the central nervous system have been described in a recent review [16]. Elevating the GH–IGF-I levels might increase muscle mass, physical strength and cognition in aging subjects. In addition, the possible role of IGF-I levels in the development of dementia has been examined in several studies. For instance, the relationship between the hypothalamus–pituitary–adrenal function, IGF-I and IGF binding proteins (IGFBP'S) was studied in patients with Alzheimer's disease (AD) [17]. Patients with AD had lowered IGF-I and IGFBP-3 levels and higher IGFBP-1 levels compared to controls. IGF-I levels correlated inversely with cognitive impairment. In another study in 49 healthy centenarians (mean age 100.4 year) cognitive functioning was assessed by clinical dementia rating [18]. Centenarians with lower IGF-I levels had higher prevalence of dementia.

The objective of the present meta-analysis was to evaluate the relationship between particularly the IGF-I status and cognition in healthy elderly by analysing the appropriate studies on this topic. Our hypothesis was that low serum IGF-I values are associated with reduced cognitive functioning in healthy elderly.

2. Methods

2.1. Search strategy

We searched the electronic databases PUBMED and Picarta from 1985 to January 2005. Studies were included if the correlation between IGF-I and cognitive functioning was described or could be calculated. The following search terms were used: IGF*, growth hormone*, memory, cognition, elderly and aging. We searched reference lists of review papers and full manuscripts were identified.

2.2. Study selection

Two investigators independently examined manuscripts for inclusion. Eligible studies were trials with quantitative data of IGF and cognitive functioning. Exclusion criteria were case reports, review articles and studies in which the psychometric quality of the used questionnaire or test was unknown.

2.3. Statistical analysis

We carried out a series of meta-analyses using a random effects model. The meta-analyses were performed using the statistical package *Comprehensive Meta-analysis* (*Copyright, 1998*, *Biostat. Inc.*, *USA*, www.meta-analysis.com) [19]. This program determines correlation coefficients (r) as effect sizes, which were pooled and analysed using a random effects model. Effect size $r = 0.1$ is defined as a small effect, $r = 0.24$ as a medium effect and $r = 0.37$ as a large effect [20]. In studies in which cognitive functioning was assessed by more than one test, we calculated one mean effect size for each study. The test for heterogeneity was calculated by the Q test.

2.4. Cognition

Cognition can be described in several ways, one of the definitions is "the intellectual or mental process whereby an organism becomes aware of or obtains knowledge." Cognitive functions are divided into a number of specific functions. Short-term memory is the ability to hold small amounts of information for several seconds, like a telephone number from the telephone book while walking to the telephone. Long-term memory is the ability to store information for a longer duration (varying from minutes to years). Executive functions are higher-order functions that make it possible to perform in situations that require several cognitive processes, like planning, response inhibition, selective attention and concept shifting. Different tests can be used to measure different parts of cognitive functioning. The mini mental state examination (MMSE), which we frequently encountered in our search, is a concise instrument to measure cognitive functioning in adults, and assesses orientation, attention, immediate and short-term recall, language and the capability to follow comments. Other frequent used tests are the digit symbol substitution test, which measures short-term memory, visual acuity,