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The Involvement of the GH/IGF-I Axis in Cognitive Functions of Adult Patients and Healthy Subjects

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Abstract: The growth hormone/insulin-like growth factor I (GH/IGF-I) axis is an important regulator of brain function which view is based on the evidence that 1) GH and IGF-I can cross the blood brain barrier, 2) GH and IGF-I can bind to sites in various brain structures, including the hippocampus, 3) GH can alter the dopamine turnover in the hippocampus and IGF-I the acetylcholine release, and 4) GH and IGF-I can activate the NMDA receptor in the hippocampus. These mechanisms may underlie the relationship between the GH/IGF-I axis and cognitive functioning. A reduced activity of the GH/IGF-I axis seems associated with cognitive dysfunction in adult patients with GH deficiency (GHD), Prader-Willi syndrome, traumatic brain injury (TBI), dementia and also with age-associated cognitive decline in healthy elderly. Moreover, IGF-I deficiency may be involved in the aetiology of schizophrenia. Treatment with GH appears to have a beneficial effect on cognitive functions in patients with GHD, Prader-Willi and TBI. However, as evidence of GH replacement on cognition in distinct groups is limited and diet, exercise, and specific medicines have known effects on the GH/IGF-I axis, future studies on the relationship between GH-, diet-, exercise-, or medication-induced GH/IGF-I increase and cognition are required.

Keywords: Growth hormone, insulin-like growth factor I, cognition, Prader Willi syndrome, traumatic brain injury, dementia, schizophrenia, leukemia.

THE GH/IGF-I AXIS AND BRAIN FUNCTION

Apart from regulating somatic growth and metabolism, it is generally acknowledged that the growth hormone/insulin-like growth factor I (GH/ IGF-I) axis plays an important role in the regulation of brain function. Currently, there is substantial evidence that GH as well as IGF-I can affect cognition and biochemical processes in the adult brain. Some cognitive effects of GH may result from the direct action of GH on the central nervous system (CNS), while other effects may be mediated by circulating IGF-I or be due to locally produced IGF-I within the brain [1]. More than a decade ago it was demonstrated in GH deficient patients that GH could pass from the circulation into the CSF [2] and another decade after this finding GH injected in mice and rats was found to cross the blood brain barrier (BBB) of these animals [3]. As in the last study no specific transport system for GH could be demonstrated, the brain influx of GH was concluded to be established by simple diffusion. Similar to GH, radiolabeled IGF-I injected in mice has been found to cross the blood brain barrier. However, with respect to IGF-I the passage is likely established by a saturable high capacity transport system instead of simple diffusion [4].

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There are binding sites for GH in brain structures such as the choroid plexus, hypothalamus and hippocampus. GH receptors located in the choroid plexus have been suggested to play a role in the receptor-mediated transport of GH across the BBB and GH receptors in the hypothalamus are likely involved in the regulatory mechanism for hormone secretion. The functions mediated by the GH receptors identified in the hippocampus may be involved in the hormone's action on memory and cognitive functions [5]. Moreover, GH treatment changes the concentration of CSF levels of the dopamine (DA) metabolite homovanillic acid (HVA) and the excitatory amino acid aspartate, a ligand for the *N*-methyl-D-aspartate (NMDA) receptor [2,6,7]. Alteration of the DA turnover in the dopamine-rich hippocampus may influence memory functions and activation of the NMDA receptor may contribute to long-term potentiation of synaptic efficacy in the hippocampus, leading to memory consolidation [8]. Indeed, le Grevès *et al*. [9] showed that GH administration in rats increases the expression of hippocampal mRNA for the NMDA subunit 2B. This finding indicates that GH may directly and indirectly (*via* aspartate) affect the hippocampal NMDA receptor.

Also for IGF-I there are specific binding sites in the brain such as in the choroid plexus, cerebral cortex, putamen, hippocampus, cerebellum, amygdala, thalamus and substantia nigra [10]. Today there is substantial evidence that

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in particular IGF-I is involved in neuroprotection, regeneration and brain plasticity [1]. The evidence is accumulating that IGF-I has important functions in the development and differentiation of the central nervous system [11] and in the modulation of growth and development of neurons in the dentate gyrus of the hippocampus [1]. In a study of van Dam *et al*. [12], levels of *N*-acetylaspartate (NAA), a marker of neuronal density and integrity, and choline, a marker of membrane synthesis were measured in adult GH deficient patients. It appeared that patients showed decreased *N*-acetylaspartate (NAA) levels and NAA/choline ratios, while plasma IGF-I was significantly correlated with brain NAA levels. The correlation between IGF-I and brain NAA indicates that IGF-I is likely to be involved in the activity of specific central nervous pathways, low IGF-I being associated with neuronal damage. In elderly subjects low IGF-I levels have been found to be associated with a poor outcome after ischemic stroke [13].This finding suggests that circulating IGF-I may influence the outcome of ischemic stroke. The importance of IGF-I for recovery after stroke has indeed been suggested by the results of studies in patients during rehabilitation after ischemic stroke. Improvement in functional and cognitive scores, as well as favorable outcome, were associated with higher IGF-I levels, which may reflect the neuroprotective role of IGF-I [14,15].

Finally, IGF-I potentiates acetylcholine release from the hippocampus [16] while Sonntag *et al*. [17] reported that IGF-I supplementation in rats appears to increase receptor subunits 2A and 2B of the hippocampal NMDA receptor.

The multiple biochemical and neurophysiological mechanisms associated with the GH/IGF-I axis strongly support the view that GH and IGF-I have an important regulatory role in brain processes.

COGNITIVE DEFICITS IN GH DEFICIENT PATIENTS

As is indicated above there is convincing evidence that the GH/IGF-I axis may directly be involved in cognitive functioning. Indeed, a number of studies have revealed that growth hormone deficiency (GHD) is associated with cognitive deficits. For instance, patients with GHD suffer from lapses of attention, difficulty in concentrating, forgetfulness, impaired spatial learning and lower perceptual speed [18-21]. Also, GH deficient patients show memory impairment, subnormal IQ scores and a low educational level. These manifestations are associated with a low IGF-I concentration, indicating that subnormal cognitive performance is specifically related to GHD [22]. Lijfijt *et al*. [23] observed impairments in selective attention and a decrease in attention-related brain potentials in GH deficient patients, possibly associated with the functioning of the anterior cingulated cortex. In another study, verbal memory as measured by the 15-word recall score, and planning behavior, processing speed and attention as measured by the trail making test were found to be impaired in GH deficient adult patients [12]. In the same year, Arwert *et al*. [24] reported a subnormal working memory speed, in particular at higher task loads, which were established during functional magnetic resonance imaging (fMRI). In contrast to the reduced speed, the quality of working memory performance appeared to be normal. The imaging data showed that patients had increased activity in dorsolateral/ventrolateral prefrontal cortex, anterior cingulate cortex, parietal cortex, supplementary motor and motor cortex, as well as in the thalamus and precuneus area. From these data it is concluded that compensatory recruitment of dorsal prefrontal brain regions is likely responsible for the normal quality of memory performance. Furthermore, from the neuropsychological and imaging data they infer that the GH/IGF-I axis may be associated with an altered prefrontal functioning in GH deficient patients.

It is important to be aware that subgroups of GHD patients may exhibit a different psychological profile. Therefore, cognitive skills should be determined specifically for childhood-onset GHD (CO-GHD) and adult-onset GHD (AO-GHD). The available data from these subgroups of patients suggest that cognitive functions are disturbed to a larger extent in patients with CO-GHD than in those with AO-GHD. This may indicate that GH and/or IGF-I are important for brain development during childhood, and possibly also in the prenatal phase [12]. Indeed, in congenital GH/IGF-I deficiency a subnormal size of the brain as expressed by the below normal head circumference has been observed [25]. Furthermore, adolescents and adults with GH insensitivity (Laron syndrome), a hereditary disease resulting in lack of IGF-I generation appear to suffer from intellectual and cognitive deficits [26] and exhibit brain abnormalities as revealed by MRI [27]. Finally, the degree of organic brain dysfunction and intellectual defects was found to correlate with mutations in the GH receptor [28].

A second distinction can be made with respect to the extent of the pituitary failure which leads to the diagnosis of isolated GHD (IGHD), in which condition only the GH secretion is insufficient, or multiple pituitary hormone deficiency (MPHD), indicating the presence of GHD in addition to an impaired secretion of other pituitary hormones (i.e. ACTH, TSH, gonadotropins). The low levels or absence of these other pituitary hormones may, even if they are replaced, impair brain function more than isolated GH deficiency. Indeed, as the distribution of IQ scores for patients with isolated growth hormone deficiency (IGHD) has been found to be in the upper and for those with multiple pituitary hormone deficiency (MPHD) in the lower part of the curve, a combined deficiency of pituitary hormones seems more harmful for the brain than GHD alone [29,30]. Thus, GHD patients do not belong to a homogenous group and cognitive deficits of these patients may be related to a subnormal brain development as a consequence of GHD in childhood or a GH-specific disturbance in neural cell metabolism due to a lowered activity of the somatotropic axis. The latter may result from traumatic brain injury or brain damage caused by a tumor and its concomitant surgical treatment and/or irradiation. Finally, inadequate replacement with thyroxin, adrenal or sex steroids may adversely affect psychological functions.

The last five years no new data on the relationship between GH deficiency and cognitive functions have become available. The data up until 2005 indicate that irrespective of the type of GHD, all patients with GH deficiency are likely to suffer from some kind of cognitive impairment. If we look at the cognitive deficits in specific subgroups of GHD patients, it seems legitimate to conclude that cognitive functions are disturbed to a larger extent in patients with CO-GHD than in those with AO-GHD. This difference may be due to the importance of GH and/or IGF-I for brain development during childhood and possibly the prenatal phase. In addition, there is some evidence that the low levels or absence of other pituitary hormones such as ACTH, TSH and gonadotropins additional to the deficiency of GH in MPHD patients may impair brain function more severely than the deficiency of unaccompanied GH in patients with isolated GH deficiency.

COGNITIVE EFFECTS OF GH REPLACEMENT IN CO-GH DEFICIENT PATIENTS

More than two decades ago the first studies on the effects of GH replacement in GH deficient adult patients were initiated. One of the first was an uncontrolled study by Almqvist *et al*. [31] reporting an improvement of memory functions after 4 weeks of GH replacement in 5 patients with CO-GHD. Some years later, the results of a double-blind, placebo-controlled crossover study of GH treatment for 12 weeks in 6 GH deficient patients indicated an absence of any beneficial effect of GH replacement on cognition [32]. In contrast to this study, results of an uncontrolled study by Sartorio *et al*. [33] showed an improved intellectual functioning in 8 CO-GHD patients after 6 months of GH therapy. These results were partly confirmed in a study in 48 CO-GHD men, with a 6-month placebo-controlled design followed by an uncontrolled 10-year period of GH treatment. There were no GH treatment effects during the placebo-controlled phase in patients whose serum IGF-I had been normalized. However, during the placebo-controlled treatment phase patients receiving supraphysiological GH treatment, that is IGF-I levels rising to a value exceeding the normal upper limit, showed memory improvements. In the group with normalised IGF-I levels, memory functioning was found to be improved after one year. From these findings it was concluded that GH treatment improves memory function in adults, while supraphysiological treatment accelerates the recovery of memory performance [34]. The memory improvements observed after one year of GH replacement appeared to be maintained after the 10 year follow-up in a remaining group of 23 men, thus implying that GH therapy has to be continued for a long period to maintain cognitive improvement and to prevent a relapse [35]. In line with these findings are the results of a preceding study on the effects of one year of GH replacement following a 1-year period of GH discontinuation in adult CO-GHD patients [36]. No improvements in memory function were found within one year of GH treatment, providing additional support for the view that a minimum treatment period of 1 year is required to improve cognitive functions.

Although the above cited data on the effects of GH replacement in CO-GHD patients up until 2005 are scarce, there are no later studies on this issue in the last 5 years. Moreover, the evidence of beneficial cognitive effects of GH treatment in this subgroup of patients is not overwhelming. From the open studies by Alqvist *et al*. [31], Sartorio *et al*. [33], Arwert *et al*. [35] and Stouthart *et al*. [36] three studies report a beneficial effect on cognition. However, the results of both placebo-controlled studies by Degerblad *et al*. [32] and Deijen *et al*. [34] indicate an absence of any GH-treatment effect, except for 6 months of supraphysiological treatment. Thus, although limited there is evidence in favour of the cognitive enhancing effects of GH replacement in adults with CO-GHD which effects may be facilitated by administering supraphysiological GH doses.

COGNITIVE EFFECTS OF GH REPLACEMENT IN AO-GH DEFICIENT PATIENTS

Also with respect to the cognitive effects of GH treatment in AO-GHD, only a handful of studies has been performed. Baum *et al*. [37] reported the results of a placebo-controlled study in GH deficient men indicating the absence of improved cognitive performance, including memory, after 18 months of GH replacement. Soares *et al*. [38] studied attention and memory performance in 9 GHD adults (2 with CO-GHD, 7 with AO-GHD) before and after 6 months of GH treatment in a placebo-controlled trial. After 6 months of treatment significant improvements were observed in diverse cognitive function tests, including memory. Partly in line with these findings are the results of an 18-month placebo-controlled study reporting improved attention after at least 3 months of GH replacement. However, even after 18 months of GH treatment the improved attention was not accompanied by improved memory performance [39].

The most recent controlled study of the cognitive effects of GH, which was also the first in elderly patients with GHD, was a placebo-controlled, parallel study in patients receiving GH or placebo for 52 weeks. The included patients were males or females aged 60-80 years. Cognitive function was assessed at weeks 0, 24 and 52 using a battery of psychometric measures. From the included 34 AO-GHD patients (22 males and 12 females) with a mean age of 66 years 16 received GH treatment and 18 placebo treatment. After 6 months the GH treated group exhibited a small improvement in memory performance as measured by the digit learning test. At the 12 month assessment, significant cognitive benefits of growth hormone were no longer found [40]. As the significant difference between GH and control group were in part due to a decline in performance in the placebo group and no effects were seen after 12 months of treatment, this study provides a quite limited evidence of a beneficial cognitive effect of GH treatment.

From the above-cited four placebo-controlled studies three provide evidence that GH improves performance in diverse cognitive domains, although effects on memory are not consistently found. Thus, with respect to GH replacement in AO-GHD patients we may conclude that evidence of beneficial cognitive effects is scarce, although the controlled character of the supportive studies makes the

treatment effects more convincing than those in CO-GH deficient patients.

THE GH/IGF-I AXIS AND GH TREATMENT IN ADULTS WITH PRADER WILLI SYNDROME

It is generally known that Prader Willi syndrome (PWS) patients exhibit mental retardation ranging from a moderate to quite substantial extent. Some studies report a mean full-scale intelligence quotient (IQ) between 50 and 70, while other studies report scores ranging from 35 to 100 or even a normal to borderline full-scale IQ score [41-47]. In addition, cognitive deficits in PWS patients has been indicated by General Intellectual Ability scores that are substantially lower than those of sibling control subjects [48]. PWS patients also show brain abnormalities, as structural MRI scans showed white matter lesions in PWS subjects in cortical, subcortical and periventricular regions. Furthermore, decreased brain volume in the parietal-occipital lobe, ventriculomegaly, Sylvian fissure abnormalities and lack of complete insula closure was described in PWS subjects [48].

Muscle mass and lean body mass have been found to be decreased in PWS patients, and fat mass increased in obese as well as non-obese patients with PWS when compared to subjects with simple obesity and a corresponding BMI [49-54]. The abnormal body composition in PWS is comparable to the body composition observed in GH deficient patients [49,51,52]. Moreover, in obese and non-obese PWS patients low levels of free IGF-I are described in addition to decreased GH secretion after pharmacological stimulation [55,56]. Thus, children and adults with PWS may exhibit GH deficiency which appears to be independent of the obese state.

It is known that cognitive functions, in particular attention and memory, are impaired in adults with GHD [57] and serum IGF-I levels in healthy elderly subjects correlate positively with cognitive performance [58]. Since part of the PWS patients are diagnosed as having GHD and show low levels of IGF-I it is worthwhile to know whether a relationship between IGF-I and cognitive functioning can also be observed in adults with PWS. Evidence of such a relationship may call for further studies that examine whether GH replacement may improve cognitive function in adults with PWS. Recently a relationship between IGF-I levels and cognition in adults with PWS was indeed established. In this study in15 adult PWS patients (4 males) with a median age of 22 years (range 19.2-42.9 years) IGF-I levels, IQ as measured by the Raven Coloured Progressive Matrices (CPM)) and cognitive function as determined by four subtests of the Cambridge Neuropsychological Automated Testing Battery(CANTAB) were compared with the measurements in 14 healthy siblings (7 males), median age 28 years (range 17.5-41.3 years). In addition, within the PWS patient group the correlation was calculated between serum IGF-I levels and cognitive measures. PWS patients were found to have lower IGF-I levels and IQ scores as well as an impaired performance on tasks measuring temporal as well as prefrontal cognitive functions. Notably, within the PWS patient group IGF-I levels appeared to correlate quite substantially (r = 0.64) with Raven IQ scores [59]. As higher IGF-I levels indeed appear to be related to better intellectual skills in PWS patients, it seems reasonable to examine whether GH treatment would improve intellectual functions in adult PWS patients. In the past years results from only one study on the cognitive effects of GH treatment in adults with Prader-Willi syndrome have been reported [43]. In this study 9 females and 10 males with a median age of 25 years were treated with GH. Half of the group had GH deficiency. After 6 months of GH treatment there were significant improvements in the TMT B test measuring cognitive flexibility and in reaction time. After 18 months of GH treatment improvements were seen in the block design test measuring perceptual organization. Thus, the results suggest that GH treatment may improve mental speed, perceptual skills and cognitive flexibility in adult patients with PWS.

THE GH/IGF-I AXIS AND GH TREATMENT IN TBI PATIENTS

Traumatic brain injury (TBI) has been found to lead to hypothalamo-hypophyseal impairment and subsequent abnormalities in hormone secretion [60,61]. The underlying pathophysiological cause for pituitary insufficiency (PI) is thought to be venous infarction following the distribution of the long hypophyseal portal veins [62]. The prevalence of pituitary/hypothalamic abnormalities after TBI has been found quite high as hypopituitarism is present in 30% to 55% of patients and severe growth hormone deficits in 15% to 20% of adult patients [63-67]. Deficiency of hormones due to hypopituitarism appears to reflect a time-dependent change of the function of the pituitary. A number of patients suffering from hypopituitarism in the acute phase of TBI, that is within 3 months after head trauma, recover in the chronic phase, although also new incidences of hypopituitarism are observed [67-70]. Aimaretti *et al*. [69] reported the occurrence of hypopituitarism after head trauma in the acute phase in 33% of the patients. In respectively 5.7%, 5.7% and 21.4% panhypopituitarism, multiple and isolated pituitary hormone deficiencies were observed. While panhypopituitarism was still seen after 12 months, the multiple and isolated deficiencies only continued in 25 % of the patients. After 12 months in 5.5 % of the patients who were not deficient in the acute phase an isolated deficiency was found. In another study the function of the pituitary recovered in 57.7 % of the posttraumatic patients after a year while new hormone deficiencies became obvious in 51.9 % of the patients [70]. In a recent study the prevalence of anterior pituitary dysfunction 12 years (SD = 8 months) after TBI was determined in 246 patients (mean age 39 years, SD = 14 yrs, 133 males). Some degree of impaired pituitary function was observed in 21 % of these patients. Total, multiple and isolated deficits were present in 1%, 2% and 18% respectively. In 5% of the patients GHD was confirmed. With respect to IGF-I, 19% had an IGF-I level that was lower than 1 SDS and 9% had an IGF-I level lower than 2 SDS [71].

Although the persisting cognitive deficits after TBI are thought to be caused by a post-contusion or post-traumatic syndrome, these impairments could also be (partly) caused

by hypopituitarism [66]. To determine whether cognitive impairments in TBI patients may be due to hormonal deficits or to the brain injury itself neuropsychological assessments were performed in 22 TBI patients (11 with isolated GH deficiency). The results indicated that TBI patients with GHD exhibited larger deficits in attention, executive functioning and memory than those without GHD [72]. These GH-related cognitive impairments in patients who develop GHD after TBI may improve with treatment of the GH deficiency. A similar study on the relationship between pituitary function and outcome from TBI concerned 72 patients (56 males; mean age 37.2 years), 10 with moderate and 52 with severe TBI. Within this group of patients 10 had GHD, while overall pituitary dysfunction occurred in 22 (30.5%) and anterior hypopituitarism in 19 (26.4%) patients. A GH peak after GHRH+ARG testing was found to correlate positively with cognitive recovery (Level of Cognitive Functioning Scale; LCFS), and a higher degree of cognitive disability as measured by the LCFS was observed in patients with hypopituitary function as compared with those with normal pituitary function. As GH peak appears an independent predictor of the improvement in cognitive abilities, a favourable outcome from TBI is likely associated with a better GH reserve [73].

The above cited studies suggest that, once hypopituitarism is diagnosed, GH treatment can improve neuropsychological performance of TBI patients. However, the last years only few studies have been performed on the effects of GH replacement on cognitive functions after TBI. One of these is a recent report on the effect of GH treatment in one GH deficient subject recovering from mild TBI [74]. The subject was a 43-year Caucasian female who had been involved in a head-on motor vehicle accident at the age of 37 years. As a consequence she suffered a mild TBI. The subject was diagnosed with adult-onset GHD and was administered with rhGH subcutaneously per day for 1 year. Neuropsychological tests were administered at baseline and after 6 and 12 months of GH treatment. To evaluate change at the individual patient level, a Reliable Change Index (RCI) methodology was employed. However, with respect to the neuropsychological evaluation reliable improvements on tests of cognition were not found. The subject only demonstrated improvements over time on a test of motor dexterity and speed. The authors attribute these findings to physical improvements observed during the study. More substantial evidence was provided by a study in 83 subjects with moderate to severe TBI. Patients, at least one year but mostly several years post-injury, were screened for GHD [75]. Out of the 43 of the 83 subjects that were found to have GHD or GH insufficiency 23 agreed to be randomized and treated with rhGH or placebo for one year. Twelve subjects received active rhGH and 11 subjects received placebo. The mean age of the placebo group was 39.1 (SD 8.5) and that of the active rhGH group 36.1 years (SD 10). Before and after treatment neuropsychological tests were administered. Differential improvements between the treatment and placebo groups was observed on four measures, i.e. simple motor speed, information processing speed, executive functioning and memory. The authors conclude, with the restriction that the data need to be interpreted cautiously due to small sample size and multiple comparisons, that cognitive impairments in persons with moderate to severe TBI may actually be the result of GHD and seems partially be reversible with GH replacement. Some minor support for this finding is provided by the results of a study in two retired amateur boxers [76]. The repetitive head trauma seemingly had a cumulative effect for the development of pituitary dysfunction as in both boxers severe isolated GHD was diagnosed. After the administration of rhGH for 6 months QoL-AGHDA scores were decreased relative to baseline, which suggest a beneficial effect of GH treatment on quality of life. Unfortunately, no cognitive functions were measured.

The above cited studies provide substantial evidence that TBI may be accompanied by GHD. As TBI patients with GHD exhibit larger cognitive deficits than those without GHD, it can be assumed that the occurrence of GHD may contribute to the harmful consequences of TBI on cognitive functioning. Moreover, the finding that even 12 years after TBI some degree of impaired pituitary function was observed in 21 % and GHD in 5% of the patients suggests that GH treatment in TBI patients may be beneficial, also in when a long period has elapsed after the traumatic injury. Unfortunately, only one study provides some evidence of positive effects of GH treatment on cognitive functions in TBI patients. More studies are needed to elucidate the magnitude of cognitive deficits in moderate to severe TBI that are the result of GHD and to examine whether these deficits are reversible with GH replacement.

GH/IGF-I AXIS AND COGNITIVE AGING IN HEALTHY ADULTS

Normal aging is accompanied with a reduced activity of the GH/ IGF-I axis. In addition, both GH deficiency and aging are characterized by the occurrence of impaired cognitive functions. After the age of 40 the amount of GH in humans progressively decreases and an increasing age-associated cognitive impairment is seen [19]. As IGF-I levels have been found associated with cognitive functioning, the reduced circulating IGF-I levels may play a role in age-related cognitive decline. Indeed, IGF-I plasma levels of healthy elderly have been found positively associated with Mini Mental State Examination (MMSE) scores [77]. Similarly, IGF-I levels in elderly healthy men were found to be associated with better performance in tests sensitive to the effects of aging, especially speed of information processing [78] and verbal fluency and MMSE [79]. With respect to age-related cognitive impairments, higher serum total IGF-I levels in healthy subjects above 55 years were associated with less cognitive decline over the following two years. In this study the Mini-Mental State Examination (MMSE) was used to assess cognitive impairment at baseline and cognitive decline after, on the average, 1.9 year of follow-up [80]. In two studies separately performed in males and females, cognitive functions of subjects of 65 years and older were related to levels of free IGF-I and IGF-I to IGFBP-3 molar ratio determined from stored blood samples. Cognitive functions were assessed by means of telephone-based tests.

Levels of free IGF-I measured in blood samples collected at a mean age of 57 years in the men were positively related to global and verbal memory performance on average of 18 years later, and IGF-I levels collected at a mean age of 56 years in women to general cognition on average of 10 years later. These results indicate that higher midlife free IGF-I may be associated with better late-life cognition [81,82]. Quite recently, low IGF-I levels were found to be associated with cognitive decline in hypertensive elderly subjects aged 65 year and older [83] and with a prolonged latency of the P300 event-related potential, which may predict cognitive decline, in males aged between 30 and 50 years [84]. The relationship between the GH/IGF-I axis and working memory performance was studied in 24 elderly males and females, aged 75-85 years. These subjects were selected from a sample of 1318 elderly subjects based on belonging to highest or lowest IGF-I quartiles. Positron emission tomography (PET) was used to measure regional blood flow during the performance of a delayed-non-matching to sample (DNMTS) working memory task. It appeared that the high IGF-I group had a higher working memory speed and a larger increase in cerebral blood flow in the left premotor and left dorsolateral prefrontal cortex. This has lead the authors to conclude that healthy elderly with high IGF-I levels exhibit a faster working memory performance and an increased recruitment of task-associated prefrontal regions [85]. Another large (n = 353) study in still older subjects determined the relationship of total serum free IGF-I and its binding protein-3 with cognitive performance in persons aged 80 years and older. After adjustment for potential confounders, individuals with verbal expression and/or comprehension problems had significantly lower IGF-I levels than subjects without cognitive impairments. Also this study supports the notion that the GH/IGF-I axis may play an important role in the age-related decline of cognitive performance [86]. In another group of subjects aged 65 to 92 years presenting no malnutrition and no inflammation plasma concentrations of IGF-I, IGF-II and IGFBP3 were found to be reduced as compared to a healthy reference group of subjects aged 20 to 65 years [87].

Quite recently the relationship between IGF-I, cognitive functioning and neuroimaging was investigated in a sample of 75 hypertensive elderly subjects aged 65 years and over. Cognitive performance was tested by the mini mental state examination (MMSE), Cambridge cognitive examination (CAMDEX-R), and the frontal assessment battery (FAB). Among other indices, free IGF-I in serum was assayed and the radial width of the temporal horn (rWTH) was determined to evaluate medial cerebral temporal lobe atrophy. Significant correlations between IGF-I levels and total as well as sub-domain scores of cognition were found. The lowest IGF-I percentile subgroup was significantly cognitively impaired. Levels of IGF-1 below 79.4 microg/l were associated with cognitive decline, whereas a level above 118 microg/l seemed to be a marker of normal cognitive performance. A statistically non-significant, but lower IGF-I level was found in the subsample with pathologically wider rWTH. This widening of the rWTH related with a decreasing IGF-I level suggests an involvement of IGF-I in hippocampus atrophy [83]. Finally, a most recent study in healthy males (mean age 61.2 years, range 50-78) reported that measures of selective attention, short-term memory and processing speed were positively associated with GH secretion [88].

The results of the above cited studies clearly support the notion that the GH/IGF-I axis may play an important role in age-related cognitive decline in healthy subjects. More specifically, there is some evidence that reduced levels of IGF-I are involved in hippocampus atrophy. Based on these findings some studies examined the effects of stimulating the activity of the GH/IGF-I axis on cognitive performance in healthy subjects. The first study investigated the stimulatory effect of an orally administered nutritional supplement, containing glycine, glutamine and niacin on the GH-IGF-I axis and cognition in healthy middle-aged and elderly subjects. Fourty-two healthy subjects (14 men and 28 women, aged 40-76 years) were enrolled in a randomized, double blind, placebo-controlled trial. They received 5 g of a nutritional supplement or placebo, twice daily orally for a period of 3 weeks. At baseline and after 3 weeks, blood was collected for measurement of serum GH and IGF-I levels and cognitive function were tested. The ingestion of the nutritional supplement for 3 weeks was found to increase serum GH levels with 70% relative to placebo, whereas circulating IGF-I levels did not change. Mean GH increased in this group from 3.23 to 4.67 mU/l. Although GH increase did not improve average cognitive performance, correlation analyses revealed that individual increases in IGF-I, but not GH, were associated with improved memory [89]. A second study investigated whether age-related cognitive decline may be arrested or partially reversed by hormonal supplementation. The effect of 6 months treatment with daily growth hormone releasing hormone (GHRH) or placebo on the cognition of a group of 89 healthy adults with a mean age of 68 years (SD = 0.7) was examined. GHRH resulted in improved performance on WAIS-R performance IQ, WAIS-R picture arrangement, finding A's, verbal sets and single-dual task. GHRH-based improvements were independent of gender, estrogen status or baseline cognitive capacity [90].

These results demonstrate that age-related cognitive impairment may be related to the age-related decline in the somatotrophic axis. They further suggest that supplementation of the somatotrophic axis may reduce cognitive decline in healthy older adults. Healthy elderly may increase the activity of the GH/IGF-I axis by diet and exercise, because these factors can affect mitochondrial energy production. Adenosine triphosphate (ATP) produced by mitochondria might activate IGF-I, which may support synaptic plasticity and cognitive function. Specifically, docosahexaenoic acid (DHA), an omega-3 fatty acid that humans mostly attain from dietary fish, can activate energy-generating metabolic pathways that subsequently affect molecules such as GF-I. As IGF-I can be produced in the liver and in skeletal muscle, as well as in the brain it can convey peripheral messages to the brain in the context of diet and exercise [91].

GH/IGF-I AXIS AND DEMENTIA

As IGF-I levels fall with aging and correlate with cognitive decline, the possible role of IGF-I levels in the development of dementia has been examined. For instance, levels of IGF-I and IGF binding proteins (IGFBP'S) were studied in patients with Alzheimer's disease (AD). Patients with AD had lowered IGF-I and IGFBP-3 levels and higher IGFBP-1 levels relative to controls. IGF-I levels inversely correlated with cognitive impairment [92]. In line with this study, recently a severe reduction of IGF-I (3.7+1.2 pg/ml after GH) was demonstrated in mild to moderate AD patients compared to age-matched healthy elderly subjects (IGF-I, 9.5+/-2.8 pg/ml after GH) [93]. In a similar study in 49 healthy centenarians (mean age 100.4 year) cognitive functioning was assessed by clinical dementia ratings. Centenarians with lower IGF-I levels had higher prevalence of dementia [94].

There is evidence that brain amyloid clearance is modulated by serum IGF-I, which levels in serum appear to be altered in Alzheimer's patients. Thus, it has been proposed that amyloid clearance by IGF-I can be a potential therapeutic target in Alzheimer's disease [95]. Moreover, when an acetylcholinesterase inhibitor, such as rivastigmine, a drug for AD, is acutely administered, the area under the curve of the GH response to GHRH doubles, showing that rivastigmine is powerful in the enhancement of GH release. Consequently, an emerging clinical target for improving the clinical manifestations of AD may be the activation of GH/IGF-I, which rejuvenates the axis, so resulting in an overall physiological benefit [96].

Currently there is only one report on the effects of increase in the activity of the somatotrophic axis on symptoms, including cognitive impairment, in patients with AD. In this double-blind, multicenter study it was examined whether the growth hormone secretagogue MK-677 (ibutamoren mesylate), a potent inducer of IGF-I secretion, reduces the rate of progression of symptoms in patients with AD. Patients with mild to moderate AD (n = 563) were randomized to receive MK-677 25 mg or placebo daily for 12 months. Efficacy measures were the Clinician's Interview Based Impression of Change with caregiver input (CIBIC-plus), the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and the Clinical Dementia Rating-sum of boxes (CDR-sob). A total of 416 patients completed treatment and assessments at 12 months. Administration of MK-677 25 mg resulted in a 60.1% increase in serum IGF-I levels at 6 weeks and a 72.9% increase at 12 months. However, there were no significant differences between the treatment groups on any of the measures over the 12 months. Despite the increase in serum IGF-I, the human growth hormone secretagogue MK-677 25 mg was ineffective at slowing the rate of progression of Alzheimer disease [97]. The absence of any effects may be due to the possibility that once the Alzheimer pathology is established induction of IGF-I may serve little purpose. Perhaps this kind of treatment needs to be tested in an early stage of the disease.

GH/IGF-I AXIS AND SCHIZOPHRENIA

It has been hypothesised that low levels of IGF-I may underlie markers of pre- and post-natal growth and development of schizophrenia. Low IGF-I levels are associated with low birth weight [98], reduced birth length, low body mass index, and at age 18 short height [99]. Additionally, evidence suggests that subnormal growth during development is associated with an increased risk of adult schizophrenia. Impaired fetal growth, famine exposure in utero, birth complications, maternal infection and childhood meningitis are associated with increased risk [100]. Such associations suggest that factors responsible for abnormal growth might influence the pathogenesis of schizophrenia [101] and because the markers of pre- and post-natal growth and development are also associated with an increased risk of schizophrenia, they imply a role for IGF-I in its aetiology [102]. With the actions of GH and IGF-I as promoters of growth in childhood [103], a disrupted GH-IGF axis may be one of the factors that underlie some of these associations [104].

In addition, schizophrenia is associated with an increased risk to develop impaired glucose tolerance, insulin resistance, and type II diabetes mellitus [105]. In line with this, an increased impaired glucose tolerance, higher levels of plasma cortisol, insulin and glucose, and a higher insulin resistance were shown in first-episode antipsychotic naïve schizophrenia patients [106]. Normally, GH promotes a rise in blood glucose level, a relative insulin resistance, and a reduction in deleterious plasma lipids, whereas IGF-I promotes a reduction in blood glucose levels and increased insulin tolerance [107]. However, a deficient IGF-I level can cause insulin resistance [108]. In order to test the hypothesis that schizophrenia patients would have significantly higher insulin resistance and lower IGF-I levels than healthy control subjects, Venkatasubramanian *et al*. [109] examined the plasma levels of glucose, insulin, IGF-I and cortisol in antipsychotic-naïve schizophrenia patients relative to healthy control subjects. Schizophrenia patients exhibited a significantly higher mean plasma insulin level, as well as significantly more insulin resistance. The mean plasma IGF-I level was significantly lower in patients and had a negative correlation with plasma insulin levels. These results support the IGF-I deficiency hypothesis as an interpretation of the aetiology of schizophrenia. It is suggested that low IGF-I levels might render the brain more vulnerable to neurodevelopmental insults potentially culminating in schizophrenia. Since IGF-I receptors are concentrated in the hippocampus, this brain region is likely to be more affected due to IGF-I deficits and alterations in this brain structure are associated with psychological disorders including schizophrenia. As a conclusion, Venkatasubramanian *et al*. [109] suggest that low levels of IGF-I might be potentially involved in the pathogenesis of schizophrenia.

With regard to the treatment of schizophrenia with antipsychotics, a longitudinal study examined the effect of antipsychotic treatment on IGF-I and cortisol in schizophrenia [110]. A reciprocal relation was found between IGF-I and cortisol. Following antipsychotic

treatment, cortisol levels decreased and IGF-I levels increased significantly in patients. The larger the reduction in cortisol level, the larger was the increase in IGF-I level. Furthermore, the larger the increase in level of IGF-I the larger was the improvement in positive symptoms. This longitudinal study point to the possibility that hypercortisolemia can result in decreased IGF-I levels. The inverse relationship between cortisol and IGF-I is already present in normal newborn infants [111]. It may be hypothesised that some effects of hypercortisolemia on the pathogenesis of schizophrenia might be mediated trough its inhibitory effects on IGF-I secretion. It is possible that decreasing the cortisol levels by antipsychotics, might result in significant elevation of IGF-I in schizophrenia patients. In accordance with the findings of Venkatasubramanian *et al*. [110], the interaction between cortisol and IGF-I supports a possible link between HPA axis abnormalities and IGF-I deficits in the pathogenesis as well as treatment of schizophrenia.

GH/IGF-I AXIS IN ADULT SURVIVORS OF CHILDHOOD LEUKEMIA

The prognosis of children with acute lymphoblastic leukemia (ALL) has improved dramatically and long-term survival rates up to 80% have been reported. Along with this development studies have been directed at identifying the neuropsychological effects of treatment for ALL in childhood. Prophylactic intrathecal (IT) chemotherapy has replaced CNS radiation therapy (CRT), as research revealed cognitive deterioration and deficits associated with such CRT [112]. However, negative effects of high-dose IT chemotherapy regimens may occur as it was reported that from 43 reviewed studies on the long-term consequences of CNS chemotherapy in ALL survivors approximately two thirds document a decline in cognitive abilities [113]. From a study by Copeland *et al*. [114] the cognitive side effects of IT chemotherapy appeared to be slightly more apparent 5 to 11 years after diagnosis than at 3-year follow-up. It may thus be assumed that cognitive impairment may be present in adult survivors of ALL who have formerly been treated with CRT or IT chemotherapy. In addition to cognitive deficits GHD or impaired GH secretion are frequently found late effects in patients treated with CRT and/or chemotherapy for childhood ALL. With respect to CRT, the prevalence of GHD was established in 75 randomly selected adult survivors of childhood ALL treated with or without cranial irradiation. The mean age of the subjects was 30 years and the mean time since ALL diagnosis was 25 years. It appeared that abnormally low GH was present in 85% of those who received past cranial irradiation. Thus, cranial irradiation was strongly related to GH deficiency and lower IGF-I levels [115]. With respect to chemotherapy, 31 patients who received chemotherapy but no CRT were selected from the medical records of 362 childhood cancer patients. Out of these patients, 17 had ALL and 1 had acute myeloid leukemia. At the initial diagnosis the median age of these 18 patients with hematological malignancies was 3.2 years, and the median age at last follow up was 17.5 years. From these patients 9 (50%) developed GH deficiency [116]. These findings indicate that GHD may occur in survivors of non-CNS tumors who receive chemotherapy without having been treated with CRT.

As GHD has been found to be associated with cognitive deficits and GH treatment may reverse these deficits, GH treatment may have positive effects on cognitive functioning in adult survivors of pediatric ALL. Based on this assumption some studies evaluated the cognitive effects of GH treatment in ALL survivors. In the first study 44 adult patients (23 males, 21 females) with a median age of 24·8 years (range 19·8-31·3) were included. They had been diagnosed with ALL at a median age of 4 years (1-17). The patients had been treated with CRT at a median of 20 years (8-27) previously and had been off chemotherapy for a median of 16·7 years (6·3-23·9). Compared to controls, the former ALL patients had a generally lower performance in neuropsychological tests, reaching statistical significance in 14 of the 20 test variables. In addition, after GH testing all patients were considered GH deficient or insufficient. Fourteen patients with severe GHD and 14 control subjects participated in a follow-up, comprising a repeat neuropsychological examination. The former ALL patients were treated during 1 year with biosynthetic human GH with median final GH dose of 0·4 mg/day (range 0·2-0·6). However, treatment with GH for 1 year in this subgroup of patients with GHD did not improve their neuropsychological performance [117].

A second study on the effects of GH treatment and neuropsychological functioning was performed in 20 adult survivors of childhood ALL with reduced bone mineral density and/or low IGF-I SD-scores (<-1 SD). A final group of 13 patients (9 males and 4 females), mean age 23.7 ± 2.9 years (range 20 - 29.7) completed a 2-year treatment with GH. Most subjects (10 of 13) had been treated with regimens including prophylactic cranial irradiation. The mean time since diagnosis was approximately 15 years. The starting dose of GH was calculated as 0.1 mg per square meters of body surface. Every two weeks, the dose was increased with 0.1 mg/m2, until IGF-I rised above 0 SD. Neuropsychological performance and IQ were assessed at pre-treatment and after one and two years. Since most participants received prophylactic cranial irradiation as part of their ALL-treatments, it was remarkable that the neuropsychological test scores of the subjects appeared to be in the normal range, while the level of intellectual functioning as determined by IQ tests was even high average. Positive treatment effects were found with respect to visual-spatial memory and attention, which functions improved after one year of treatment. Correlation analysis indicated that improvement of visual-spatial memory was related to the IGF-I increase in the first treatment year. In addition, verbal memory functions were found to be negatively affected by GH treatment. As results of the study suggest that relationships between GH therapy and neuropsychological functioning seem strongly dependent on IGF-I levels and an excessive increase of IGF-I seems adversely affect verbal memory performance, the authors presume that a lower dose of GH may be more effective to enhance cognitive functions in ALL survivors [118].

CONCLUSION

Current knowledge provides abundant evidence that the GH/IGF-I axis is an important regulator of brain function. The evidence is based on the knowledge that: 1) GH and IGF-I can cross the blood brain barrier, respectively by simple diffusion or by a saturable high capacity transport system, 2) for GH as well as IGF-I there are binding sites in various brain structures, including structures that are involved in cognitive functions, like the hippocampus, 3) within the hippocampus the DA turnover is altered by GH and the acetylcholine release by IGF-I, and 4) GH and IGF-I likely contribute to long-term potentiation of synaptic efficacy in the hippocampus by activating the NMDA receptor. On a behavioural level, there is evidence that the biochemical and neurophysiological mechanisms associated with the activity of the GH/IGF-I axis may directly affect cognitive functioning. Indeed, the reduced activity of the GH/IGF-I axis appears to be related with impaired cognitive function in a diversity of groups of subjects with intellectual disabilities such as patients with GHD, Prader-Willi syndrome, TBI, dementia but also in healthy adults. Moreover, IGF-I deficiency may be involved in the aetiology of schizophrenia. As a consequence, the effects of GH treatment on cognitive functions have been examined in patient groups and healthy elderly subjects. Although the results of studies are contradictory, the general finding in patients with GHD, Prader-Willi and TBI are in favour of a beneficial effect of GH replacement in case of pituitary dysfunction. From a number of 14 studies on the effects of GH replacement in a diversity of patient groups 10 reported positive effects of GH replacement on cognition. The available data suggest that a treatment period of approximately one year is required to improve cognitive functions and that GH therapy has to be continued to maintain cognitive improvement and to prevent a relapse.

In spite of the quite large body of literature on the cognitive effects of GH deficiency the number of studies on the cognitive effects of GH replacement in distinct groups of patients with GHD is still quite limited. Moreover, diet, exercise, acetylcholinesterase inhibitors which are prescribed in Alzheimer's disease and antipsychotic treatments have known effects on the GH/IGF-I axis. Studies on the relationship between diet-, exercise-, or medication-induced GH/IGF-I increase and cognition may be useful to explain how these interventions affect brain functions.

The current knowledge indicates that disturbances of the activity of the GH/IGF-I axis may impede optimal brain development and function and even be involved in the development of schizophrenia and dementia. Moreover, it seems justified to assume that GH replacement may directly, and diet, exercise as well as anti-dementia or antipsychotic medication may indirectly affect the activity of the GH/IGF-I axis. The use of GH and IGF-I as therapeutic tools for CNS related impairment in conditions with altered GH/IGF-I may be expected to increase in the future. It may well be true that supplementation with GH or IGF-I can be used to reduce the risk of the development of schizophrenia and dementia and to attenuate the cognitive sequelae of TBI and ischemic stroke.

Yet, it seems that the number of studies in this field is progressively decreasing which may reflect a reduced scientific interest in the role of the GH/IGF-I axis in maintaining optimal brain function and intellectual performance. To expand the current knowledge more scientific research on the involvement of GH deficiency in the development of cognitive disorders and the potential of GH therapy to slow down cognitive deterioration in diverse patient groups with GHD is highly required.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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