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Insulin-like growth factor-I, cognition and brain aging

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Abstract

Aging is associated with a decline in the activity of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis. As aging also coincides with a decline in specific cognitive functions and as some of these dysfunctions are also observed in subjects with GH deficiency, it has been hypothesised that a causal relationship exists between the reduction in circulating GH and/or IGF-I and the observed cognitive deficits in the elderly. The present review summarises the available data concerning the possible relation between GH, IGF-I and cognitive performance, and regarding possible underlying pathophysiological mechanisms.

Keywords: Insulin-like growth factor-I; Growth hormone; Aging; Cognition

1. Introduction

Age-related decline in cognitive functions has been extensively documented in several domains (Dal Forno and Kawas, 1995; La Rue, 1992). Specific cognitive abilities have been found to be relatively vulnerable to aging. This particularly concerns attention, long-term memory and executive functioning (concept shifting, planning and mental flexibility). The activity of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis declines with advancing age (Lamberts et al., 1997). Indeed, it has been speculated that this relative hyposomatotropism that coincides with aging may contribute to the age-related decline in cognitive functioning (Van Dam et al., 2000). This hypothesis is supported by two observations. Firstly, there is ample evidence, mainly form animal and in vitro studies, that IGF-I plays a role in neuronal cell functioning (Bondy and Cheng, 2004). As significant numbers of IGF-I receptors have been demonstrated in those areas in the central nervous system which are essential for cognitive performance, e.g. the hippocampus and the prefrontal cortex, the supposition that declining local and systemic IGF-I concentrations in the elderly contribute to attenuated performance of these brain areas seems logical. Secondly, reduced cognitive performance has been demonstrated in small patient groups with GH deficiency, who have highly reduced IGF-I levels both in plasma and in the central nervous system (Van Dam et al., 2000). In recent years, more researchers have focused on the interaction between the hormones of the somatotropic axis and the central nervous system (Schneider et al., 2003). In the present review, we will give an overview of the available information regarding the association between attenuated IGF-I secretion (both in the elderly and in GH-deficient patients) and cognitive performance. As the possible underlying mechanisms regarding IGF-I receptor signaling and molecular and cellular mechanisms in the brain are discussed elsewhere in the present special issue of this journal (Bondy and Cheng, 2004), we will primarily focus on human studies regarding the association between the somatotropic axis and cognitive performance.

2. The somatotropic axis and the IGFs in the elderly

High plasma IGF-I concentrations are normally observed during puberty. During further life, plasma IGF-I declines

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significantly, from approximately 400 ng/ml at the age of 15 years to approximately 100 ng/ml at the age of 75 years. A rapid decline is observed during the first years after puberty, but a further reduction of approximately 100 ng/ml is observed between the ages of 30 and 75 (Strasburger et al., 2001). In normal physiology, plasma IGF-I reflects primarily hepatic IGF-I synthesis, which depends upon pituitary GH secretion. It has been clearly demonstrated that the decline in plasma IGF-I throughout life occurs simultaneously with a decline in pituitary GH secretion and circulating plasma GH levels. Many authors have suggested that this decline in the activity of the somatotropic axis contributes to a variety of pathophysiological and functional changes which are often associated with aging, e.g. reduced muscle mass, increased visceral fat mass, attenuated bone mineral density, cardiovascular changes, reduced elasticity of the skin and cognitive performance (Lamberts et al., 1997; Van Dam et al., 2000). The supposed contribution of hyposomatotropism to reduced quality of life in the elderly has even led to an aggressive promotion of commercially available GH preparations, in particular in the United States. However, the evidence of clinical benefits of GH administration is still virtually absent and the risks of the use of GH as a lifestyle drug have not yet been assessed in a healthy elderly population.

Besides this age-associated overall decline in plasma IGF-I when large groups of healthy individuals are compared, important differences in IGF-I levels and GH secretion exist between subjects of the same age and sex. These differences are probably the result of a combination of factors, which affect the activity of the GH/IGF-I axis, e.g. dietary habits, liver function, body composition, circulating free fatty acids, physical activity and/or genetic differences. The clinical relevance of these differences is still a matter of debate. Most of our current knowledge regarding the impact of decreased activity of the somatotropic axis on body composition, lipid profile, bone mineral content, muscle mass, cognitive function or quality of life has been acquired by studying patients with GH deficiency (Verhelst and Abs, 2002). It seems very tempting to extrapolate these findings when interpreting the variations in GH and IGF-I secretion in normal physiology and their clinical relevance. However, it should be remarked that GH deficiency is a defined clinical condition, and that its clinical characteristics should not be incorporated in the continuum of GH/IGF-I secretion in normal physiology. Except for the possible contribution to cognitive functioning, data regarding the clinical relevance of variations in the activity of the somatotropic axis as well as underlying mechanisms are beyond the scope of this review and will not be discussed further.

In summary, although on average aging is associated with reduced activity of the GH/IGF-I axis, substantial inter-individual differences are observed. The possible interaction between GH, IGF-I and the central nervous system is an interesting base to study the hypothesis that these inter-individual differences in somatotropic axis activity contribute to the cognitive changes, which are associated with aging.

3. Interaction between GH, IGF and the central nervous system

IGF-I receptors have been demonstrated in different areas of the human brain, with highest concentrations in the hippocampus, amygdala and parahippocampal gyrus (Adem et al., 1989). Activation of these receptors may be associated with different functions, including growth and development of the brain, normal brain physiology and metabolism, and regulation of nerve cell maintenance and repair either during aging or after traumatic or ischemic injury. Clinical and experimental studies have demonstrated that increased systemic GH and IGF-I levels lead to a rise in IGF-I concentrations in the cerebrospinal fluid (Pulford and Ishii, 2001). Systemic IGF-I has been shown to influence central nervous system physiology, and thus acts across the blood–brain barrier (Pulford et al., 1999). Besides central effects of systemic IGF-I, local IGF-I synthesis occurs in most areas of the brain and may thus have direct metabolic and neurophysiologic effects (Johansson and Bengtsson, 1997; Han, 1995).

Metabolic effects of IGF-I in different brain areas have been studied primarily in rodents and are discussed elsewhere in this issue. In summary, it has been demonstrated that IGF-I, either systemic or locally produced, plays a neuroprotective role by various mechanisms, of which stimulation of neuronal acetylcholine release (Araujo et al., 1989; Nilsson et al., 1988), activation of the *N*-methyl-D-aspartate (NMDA) receptor and (possibly subsequent) stimulation of glucose utilisation seem to be the most important. It is unclear whether the observed stimulation by IGF-I of neurite formation and oligodendrocyte proliferation (Lynch et al., 2001; McMorris et al., 1986) is the outcome of activation of these pathways only or also mediated by other mechanisms.

As the most important brain areas associated with cognitive deficits are the medial temporal lobe, in particular the hippocampus and parahippocampal areas, and the prefrontal cortex (Erickson and Barnes, 2003), the interaction between IGF-I and these areas is of particular interest for the scope of this review. As stated before, these areas have the highest concentrations of IGF-I receptors in the human brain. It has recently been demonstrated that the levels of IGF-I receptors in the CA1 and CA3 regions of the hippocampus, the cortex and the molecular layer of the dentate gyrus are upregulated in aged rats (Chung et al., 2002). Additionally, it was reported that hippocampal IGF-I receptor mRNA concentrations were increased with age and positively correlated with learning deficits in aged rats (Stenvers et al., 1996). These data suggest that the areas in the central nervous

system which are particularly vulnerable to IGF-I deficits can partially adapt to the condition of relative hyposomatotropism of aging. It should be remarked that the finding by Chung et al. is in contrast with earlier observations which showed no alterations in IGF-I binding sites in the hippocampus of aged rodents (D'Costa et al., 1995; Dore et al., 1997; Sonntag et al., 1999). IGF-I receptor densities in human frontal cortex were found to be higher in neonates than in adults, without further change during aging (De Keyser et al., 1994).

Some studies have focused on the effect of IGF-I treatment in older rodents on cognitive function and neuronal regeneration. Cognitive performance, e.g. performance in the Morris water-maze task, has been shown to improve following intracerebroventricular infusion of IGF-I (Markowska et al., 1998). These improvements were associated with a correction of attenuated hippocampal NMDA-2A and NMDA-2B receptors in aged rats (Sonntag et al., 2000a), with a correction of attenuated neurogenesis in the dentate gyrus (Lichtenwalner et al., 2001) and in the hippocampus (Aberg et al., 2000), but not with changes in neuronal or synapse density in the CA3 region of the hippocampus, which seems to be less affected by aging (Poe et al., 2001). Besides neuronal regeneration and neurotransmitter activity, the age-related decrease in glucose utilisation of different areas of the brain including the hippocampus could be reversed by intracerebroventricular IGF-I administration (Aberg et al., 2000). Furthermore, it has been suggested that microvascular supply of different brain areas may be stimulated by IGF-I (Sonntag et al., 2000b). Similar effects, which are probably mediated by IGF-I, have been observed by Le Greves et al. (2002), who administered subcutaneous GH to aged rats and observed increased NMDA-2B (but not 2A) receptor mRNA levels in the hippocampus.

GH probably plays a major role in stimulating local IGF-I synthesis. In humans, GH receptors are found throughout the brain, but are mainly concentrated in the chorioid plexus, hippocampus, putamen and hypothalamus (Lai et al., 1991, 1993; Bennett and Robinson, 2000). The high numbers of GH receptors in the hippocampus (approximately two- to four-fold higher than in most other areas of the brain) suggests that GH plays a relatively important role in hippocampal functions. Both human and animal studies demonstrate that the number of GH receptors declines with age throughout the brain (Lai et al., 1991, 1993; Nyberg, 1997; Zhai et al., 1994). This could support the hypothesis that changes in the GH/GH-receptor interaction associated with aging contribute to alterations in functioning of different brain areas, in particular the hippocampus. Scheepens et al. (2001) demonstrated that GH treatment can partly protect the hippocampus, frontoparietal cortex and dorsolateral thalamus against the consequences of a hypoxic-ischemic injury in rats. They suggest that these protective effects are mediated directly by activation of the GH receptor, and not by stimulation of IGF-I synthesis.

4. Possible contribution of the IGFs to cognitive function

The number of clinical studies focusing on the possible relationship between the hormones of the somatotropic axis and cognition is limited. The available studies can be divided in those who have assessed cognitive function in patients with GH deficiency (both childhood- and adulthood-onset) and those who have evaluated correlations between circulating IGF-I and cognitive performance in normal physiology, in particular during the aging process. As a significant number of different cognitive processes have been defined, and as these processes probably originate in different brain areas and may be less or more affected by the aging process, studies which have focused on these specific age-related cognitive functions are of particular interest.

4.1. IGF-I and cognitive performance during aging

As stated above, plasma IGF-I levels decline with age, but large inter-individual differences can be observed between individuals of the same age and sex. As defects in cognitive performance also vary significantly between individuals of the same age, and as certain cognitive functions decline to a greater extent than others during aging, we previously focused on these inter-individual differences in aging men. We observed an association between plasma IGF-I levels and age-sensitive cognitive function, particularly cognitive speed and motor performance (Aleman et al., 1999, 2001). In addition, we demonstrated a dissociation between IGF-I levels and maximal pituitary GH secretion as correlates of cognitive function, particularly perceptual motor speed and mental processing speed (Aleman et al., 2000). Vitiello et al. (1999) reported similar findings regarding the correlation between IGF-I and the results of age-sensitive performance tests that involve problem-solving abilities. Papadakis et al. (1995) found a significant association between IGF-I levels and a measure of mental processing speed, but not with another speeded test of executive cognitive function. Recently, Cherrier et al. (2004) reported an association between IGF-I and IGF-II levels and spatial reasoning and memory and verbal fluency after 6 weeks of testosterone administration in 25 healthy older men (ranging from 50 to 80 years). The association between IGF and cognition was independent of testosterone. A similar association between IGF-I levels and cognitive function as measured by the Mini Mental State Examination (MMSE) has been observed in elderly individuals with different degrees of mild cognitive impairment (Rollero et al., 1998). No associations between GH secretion and cognition were observed in this study. Kalmijn et al. (2000) reported an association between plasma IGF-I and IGF-I/IGF-binding protein 3 ratios and performance on a mini mental state examination in elderly subjects. A similar association between IGF-I and information processing speed in elderly subjects was

reported by Dik et al. (2003). These authors investigated whether IGF-I was associated with cognitive performance and 3-year cognitive decline in 1318 subjects, aged 65–88 years. Analysis in quintiles of IGF-I revealed a threshold effect of low IGF-I on information processing speed, with lower speed in subjects in the lowest quintile of IGF-I (<9.4 nmol/l) versus those in the other four quintiles. This threshold of low IGF-I was also observed for 3-year decline in information processing speed. Thus, this study suggests that IGF-I levels below 9.4 nmol/l are negatively associated with both the level and decline of information processing speed. Significant correlations between the IGF-I:GH ratio and cognitive performance (in particular visual and verbal memory) were reported by Morley et al. (1997) in men ranging from 20 to 84 years. Paolisso et al. (1997) observed a positive correlation between IGF-I/IGF-BP3 ratios and mini mental state performance in healthy centenarians, suggesting that free IGF-I may be the determining factor to understand the association between the somatotropic axis and cognitive performance.

In summary, the available data indicate that higher plasma levels of IGF-I in elderly subjects are associated with better performance on neuropsychological tests evaluating different cognitive functions normally affected by age, including visual and verbal memory, processing motor speed and cognitive performance, and executive cognitive function. However, all studies that have been published so far are correlational observations, and have in most cases not been corrected for other important variables such as physical fitness or other physiological factors which influence plasma total IGF-I levels, e.g. sex steroid or thyroid hormone levels, liver or kidney function, or circulating levels of IGF binding proteins. Therefore, it should not be excluded that the observed associations only reflect causal relationships between other determinants which have an impact on both circulating total IGF-I levels and cognitive performance. This problem may be clarified either by multivariate analysis, which would imply the study of large populations or longitudinal observational studies, or intervention studies with the objective to increase circulating IGF-I. Papadakis et al. (1996) reported marginal effects of 6 months of GH treatment in 52 elderly healthy men on performance on the Trails B test, a test reflecting perceptual motor speed and a trend towards improvement on the Mini Mental State examination, but no improvement on the Digit Symbol Substitution score, which evaluates cognitive and perceptual-motor processing speed. In a second intervention study, one year IGF treatment in 24 elderly women did not lead to an improvement in memory performance (name–face and word-list recall), depressive state (Geriatric Depression Scale), anxiety (State Trait Anxiety Inventory) or sleep (Friedlander et al., 2001). No other intervention studies have been reported yet. The available data regarding the possible relation between the somatotropic axis and cognitive decline during aging have been summarized in Table 1.

4.2. Cognitive function in GH deficiency

GH deficiency is a condition associated with reduced circulating GH and IGF-I levels. The development of GH deficiency may occur during embryogenesis or childhood, either idiopathic or as a consequence of pituitary or hypothalamic disease (childhood-onset GH deficiency) or during adult life, mostly as a consequence of a pituitary disease (adulthood-onset GH deficiency). GH deficiency may occur either isolated or in conjunction with other pituitary hormone deficits. Childhood-onset GH deficiency is mostly diagnosed in children with growth retardation, while adulthood-onset GH deficiency is usually detected in patients after a pituitary disease has been discovered, and is associated with alterations in body composition, increased visceral fat mass, reduced bone and muscle mass, and reduced physical fitness and quality of life. Both childhood-onset GH deficiency and adulthood-onset GH deficiency are currently treated with recombinant human GH with the objective to achieve normal physiological IGF-I levels. This treatment leads to correction of growth retardation as well as to improvement of the symptoms with adulthood-onset GH deficiency. As GH deficiency is associated with reduced GH and IGF-I levels in cerebrospinal fluid, and as GH treatment corrects these parameters (Johansson et al., 1995; Johansson and Bengtsson, 1997), GH-deficient patients are an interesting population to study the effects of GH and IGF-I on the brain, and in particular on cognitive function (Sartorio et al., 1996; Van Dam et al., 2000). If alterations in IGF-I availability indeed contribute to cognitive decline during aging, GH deficiency may be considered as a model for accelerated brain aging, and alterations in cognitive performance in these patients may be of particular interest.

A limited number of studies have focused on cognitive function in childhood-onset GH deficiency or adulthood-onset GH deficiency subjects. Deijen et al. (1996) demonstrated impaired memory performance (short-term, long-term and iconic memory) and lower intelligence scores in a group of 48 adults with childhood-onset GH deficiency. Perceptual motor performance and emotional well-being were disturbed only in GH-deficient men with multiple (substituted) pituitary hormone deficits, but not in men with isolated GH deficiency. Therefore, the authors suggest that cognitive defects, but not alterations in mood and general well-being are associated with the GH-deficient state. In an intervention study in the same patient group, the authors demonstrated a normalisation of memory performance, but not of perceptual motor skill or emotional well-being after two years of GH treatment (Deijen et al., 1998). Other, smaller studies evaluating the effect of GH substitution on cognitive function in childhood-onset GH deficiency are contradictional and difficult to interpret, but suggest a possible role of the somatotropic axis in performance on non-verbal intelligence and recognition memory (Degerblad et al., 1990; Almqvist et al., 1986; Sartorio et al., 1995). A recent study reported on the effects of a 6-month interven-

Table 1
Studies of the relation between IGF-I and cognitive function in elderly adults

Study	*N*	Age (years)	Cognitive functions	Findings	Comments
Papadakis et al., 1995	104	74–94	Mental processing speed, executive cognitive function	Significant association between IGF-I levels and a measure of mental processing speed, but not with the speeded test of executive function	
Morley et al., 1997	65	20–84	Visual memory, verbal memory (word-list recall), animal naming	Significant correlations of IGF-I/GH with visual and verbal memory	
Paolisso et al., 1997	79	<50 (*N*=30), 75–99 (*N*=30), >100 (*N*=19)	Mini-Mental State Examination (MMSE)	Significant correlations of IGF-I with MMSE in the two elderly groups (>75 years)	
Rollero et al., 1998	22	65–86	MMSE	IGF-I levels were directly correlated with MMSE scores, being lowered in patients with more advanced cognitive deterioration	Included subjects with mild cognitive impairment
Aleman et al., 1999	25	65–76	Vocabulary, mental processing speed, executive function, verbal memory (word-list recall), spatial ability	Significant correlations of IGF-I with mental processing speed and executive function	Adjusted for confounding effects of level of education
Kalmijn et al., 2000	186	55–80	MMSE	In this prospective study higher serum total IGF-I levels and higher total IGF-I/IGFBP-3 ratios, but not higher free IGF-I levels, were associated with less cognitive decline over the following 2 years	Adjustment for age, sex, education, body mass index and fasting insulin levels
Friedlander et al., 2001	16	70.6 ± 2	Memory for face–name associations and word-list recall	No effects on memory after 1 year of IGF-1 therapy, compared to placebo	Randomized controlled trial of IGF-1 substitution
Dik et al., 2003	1318	65–88	Information processing speed, memory, fluid intelligence and MMSE	No correlations between IGF-1 and cognitive function across the whole sample, but IGF-I levels below 9.4 nmol/l were negatively associated with both the level and decline of information processing speed	

tion with GH replacement in 18 hypopituitary patients with adulthood-onset GH deficiency (Holsboer et al., in press). After 6 months, a significant improvement was observed in attentional functioning compared to placebo. In contrast, verbal memory and non-verbal intelligence did not improve.

Besides these intervention studies, additional information exists regarding cognitive and emotional functions in children with disturbances of the somatotropic axis. For example, Kranzler et al. (1998) evaluated intelligence in a group of 18 Ecuadorian school children with IGF-I deficiency as a consequence of a mutation of the GH receptor. They demonstrated that no difference existed between these patients and a control group when nonverbal psychometric and chronometric tests of intelligence were used. These tests included speed and efficiency of elementary cognitive processing. In an earlier study in Ecuadorian school children with IGF-I deficiency, exceptional school performance was observed (Rosenbloom et al., 1990). In contrast, attenuated intellectual abilities were reported in Israelian patients with GH receptor mutations and subsequent IGF-I deficiency (Laron and Parks, 1993). Abbott et al. (1982) earlier reported low-normal verbal, nonverbal and overall intellectual abilities in 11 GH-deficient children with different underlying conditions. The observed cognitive difficulties may not be related to the GH-deficient state only, but also to the psychological impact of growth retardation on intelligence and school performance (Stabler et al., 1991). Therefore, it remains extremely complex to study the interaction between the somatotropic axis and cognitive functioning by studying children with GH deficiency.

Using electrophysiological measurement of event related brain potentials, we recently demonstrated that adults with

childhood-onset GH deficiency have attentional deficits in association with reduced N2b depolarisation (Lijffijt et al., 2003) (Fig. 1). Alterations in N2b are associated with functional deficits in the cingulate cortex, and are also observed in the aging population. In addition, we could demonstrate small cognitive deficits, which were identified as attenuated performance on a delayed verbal memory test and a test evaluating processing speed and planning behaviour (Trails A). Furthermore, plasma IGF-I levels in these patients were correlated with *N*-acetylaspartate/choline levels in the brain, which suggests an inverse association between circulating IGF-I levels and neuronal damage (Van Dam et al., 2002). These observations are in line with the finding that GH substitution in adulthood-onset GH deficiency subjects is followed by an increase in aspartate levels in the cerebrospinal fluid (Burman et al., 1996).

Adulthood-onset GH deficiency has been associated with other forms of cognitive dysfunction, in particular attenuated cognitive ability. Baum et al. (1998) were the first to report on 40 men with adulthood-onset GH deficiency, either isolated or combined with other pituitary deficits. They reported reduced verbal learning and visual memory scores in comparison with normal controls, but normal performance on a variety of other cognitive tasks, suggesting a mild deficit in the ability to learn and remember new information as a consequence of adulthood-onset GH deficiency. As they did not report any improvement in the observed cognitive deficits after 18 months of GH substitution, the specific contribution of the GH/IGF-I axis for the observed deficits remains uncertain. Other factors, e.g. pituitary radiotherapy or other pituitary hormone deficits, could also play a role.

Other studies regarding the impact of GH deficiency on cognitive function in adults with pituitary disease have followed. Soares et al. (1999) demonstrated an improvement in picture arrangement, vocabulary, comprehension and verbal fluency after 6 months of open-label GH treatment. A major drawback of their study was the absence of a significant effect on cognition during the placebo-controlled phase, which preceded the open-label treatment period. Bülow et al. (2002) studied adult hypopituitary women with GH deficiency, and demonstrated attenuated performance on tests evaluating vocabulary, information processing speed, spatial learning and reaction time. They also reported a larger proportion of mental disorders in the hypopituitary women, despite substitution of all hormonal deficits except GH. Peace et al. (1998) observed impaired memory and executive function in a group of GH-deficient patients with pituitary disease who had been operated (either transcranially or transsphenoidally), but also showed that those GH-

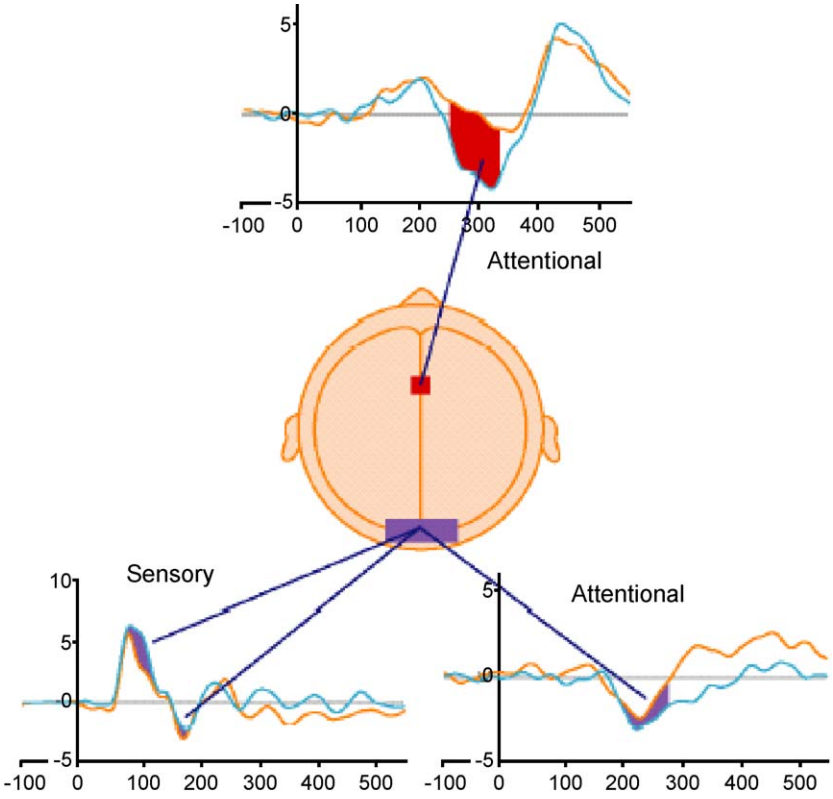

Fig. 1. The traces represent event-related potential difference waves constructed in such way that they reflect sensory and attentional processes, respectively (orange: childhood-onset growth hormone (GH) deficiency; blue: controls). Event-related potentials bottom left: sensory processes over posterior visual cortex (Oz). Bottom right: attentional process over posterior visual cortex (Oz). Event-related potentials above the model of the head: attentional process, over anterior areas (Fz), that differed significantly between the two groups. The red area indicates a significant difference between childhood-onset GH deficiency and control; blue areas represent non-significant differences between the two groups. Reprinted with permission from Lijffijt et al. (2003).

deficient patients who had not been operated performed suboptimally on tests requiring high levels of cognitive processing only. In summary, only a few studies regarding cognitive function in adulthood-onset GH deficiency subjects have been carried out. The available data indicate that more severe cognitive deficits are found in patients with more extended pituitary disease, reflected by more invasive surgery or radiotherapy. As the information regarding the effect of GH substitution on these cognitive parameters is limited, and as the evidence regarding the effect of this intervention is sparse and contradictory, additional placebo-controlled studies are needed for further clarification of this clinically relevant issue.

5. Summary and conclusions

Animal and in vitro studies have clearly demonstrated that an interaction exists between IGF-I and the central nervous system. Additional evidence exists regarding the direct effects of GH on the brain, although it has proven to be difficult to detach the physiological effects of GH from IGF-I, both because of the systemic effect of GH on IGF-I synthesis and as a consequence of the possible contribution of GH to local IGF-I production in the brain. The hippocampus seems to be a primary target for IGF-I, which supports the hypothesis that IGF-I and/or GH contribute to cognitive performance. Clinical studies are available, but limited, and the outcome of these studies is not unequivocal. There seems to be an association between circulating IGF-I levels and cognitive performance in the elderly. Furthermore, similar associations between cognitive performance and the somatotropic axis have been observed in GH-deficient subjects, although the number of patients studied is limited and associated hormonal deficits may play a role. In addition, these patients have usually undergone surgery or radiotherapy, which may hamper the interpretation of the available data. It should be remarked, however, that GH-deficient patients remain the only available patient group, which allows us to unravel the interaction between GH, IGF-I and the brain in a clinical setting. Therefore, larger clinical placebo-controlled studies in these patients are needed. At present, additional techniques allow us to investigate the interaction between the hormones of the somatotropic axis and the brain using non-invasive techniques. Such studies should tell us more about underlying mechanisms and may subsequently learn more about cognitive deterioration in the elderly. Although GH treatment in healthy elderly subjects is probably not an attractive tool to intervene in the normal physiology of aging, and is even potentially harmful, methods may be developed to increase the endogenous GH secretion and subsequent IGF-I synthesis in the elderly. We should, however, not anticipate on the outcome of such studies by supporting GH treatment in healthy elderly, but carefully proceed with additional studies in this field.

References

Abbott, D., Rotnem, D., Genel, M., Cohen, D.J., 1982. Cognitive and emotional functioning in hypopituitary short-statured children. Schizophr. Bull. 8, 310–319.

Aberg, M.A., Aberg, N.D., Hedbacker, H., Oscarsson, J., Eriksson, P.S., 2000. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J. Neurosci. 20, 2896–2903.

Adem, A., Jossan, S.S., d'Argy, R., Gillberg, P.G., Nordberg, A., Winblad, B., Sara, V., 1989. Insulin-like growth factor 1 (IGF-1) receptors in the human brain: quantitative autoradiographic localization. Brain Res. 503, 299–303.

Aleman, A., Verhaar, H.J., de Haan, E.H.F., de Vries, W., Samson, M.M., Drent, M.L., van der Veen, E.A., Koppeschaar, H.P.F., 1999. Insulin-like growth factor-I and cognitive function in healthy older men. J. Clin. Endocrinol. Metab. 84, 471–475.

Aleman, A., de Vries, W.R., de Haan, E.H.F., Verhaar, H.J.J., Samson, M.M., Koppeschaar, H.P.F., 2000. Age-sensitive cognitive function, growth hormone and insulin-like growth factor 1 plasma levels in healthy older men. Neuropsychobiology 41, 73–78.

Aleman, A., de Vries, W.R., Koppeschaar, H.P.F., Osman-Dualeh, M., Verhaar, H.J.J., Samson, M.M., Bol, E., de Haan, E.H.F., 2001. Relationship between circulating levels of sex hormones and insulin-like growth factor-I and fluid intelligence in older men. Exp. Aging Res. 27, 283–291.

Almqvist, O., Thoren, M., Saaf, M., Eriksson, O., 1986. Effects of growth hormone substitution on mental performance in adults with growth hormone deficiency: a pilot study. Psychoneuroendocrinology 11, 347–352.

Araujo, D.M., Lapchak, P.A., Collier, B., Chabot, J.G., Quirion, R., 1989. Insulin-like growth factor-1 (somatomedin-C) receptors in the rat brain: distribution and interaction with the hippocampal cholinergic system. Brain Res. 484, 130–138.

Baum, H.B., Katznelson, L., Sherman, J.C., Biller, B.M., Hayden, D.L., Schoenfeld, D.A., Cannistraro, K.E., Klibanski, A., 1998. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. J. Clin. Endocrinol. Metab. 83, 3184–3189.

Bennett, P.A., Robinson, I.C.A.F., 2000. The central nervous system as a direct target for growth hormone action. In: Smith, R.G., Thorner, M.O. (Eds.), Human Growth Hormone: Basic and Clinical Research. Humana Press, Totowa, NJ, pp. 145–162.

Bondy, C.A., Cheng, C.M., 2004. Signaling by insulin-like growth factor 1 in brain. Eur. J. Pharmacol. 490, 25–31.

Bülow, B., Hagmar, L., Orbaek, P., Osterberg, K., Erfurth, E.M., 2002. High incidence of mental disorders, reduced mental well-being and cognitive function in hypopituitary women with GH deficiency treated for pituitary disease. Clin. Endocrinol. (Oxf.) 56, 183–193.

Burman, P., Hetta, J., Wide, L., Mansson, J.E., Ekman, R., Karlsson, F.A., 1996. Growth hormone treatment affects brain neurotransmitters and thyroxine. Clin. Endocrinol. (Oxf.) 44, 319–324.

Cherrier, M.M., Plymate, S., Mohan, S., Asthana, S., Matsumoto, A.M., Bremner, W., Peskind, E., Raskind, M.A., LaTendresse, S., Haley, A.P., Craft, S., 2004. Relationship between testosterone supplementation and insulin-like growth factor-I levels and cognition in healthy older men. Psychoneuroendocrinology 29, 65–82.

Chung, Y.H., Shin, C.M., Joo, K.M., Kim, M.J., Cha, C.I., 2002. Region-specific alterations in insulin-like growth factor receptor type I in the cerebral cortex and hippocampus of aged rats. Brain Res. 946, 307–313.

Dal Forno, G., Kawas, C.H., 1995. Cognitive problems in the elderly. Curr. Opin. Neurol. 8, 256–261.

D'Costa, A.P., Xu, X., Ingram, R.L., Sonntag, W.E., 1995. Insulin-like growth factor-1 stimulation of protein synthesis is attenuated in cerebral cortex of aging rats. Neuroscience 65, 805–813.

Degerblad, M., Almqvist, O., Grunditz, R., Hall, K., Kaijser, L., Knutsson, E., Ringertz, H., Thoren, M., 1990. Physical and psychological capabilities during substitution therapy with recombinant growth hormone in

adults with growth hormone deficiency. Acta Endocrinol. Copenh. 123, 185–193.

Deijen, J.B., de Boer, H., Blok, G.J., van der Veen, E.A., 1996. Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 21, 313–322.

Deijen, J.B., de Boer, H., van der Veen, E.A., 1998. Cognitive changes during growth hormone replacement in adult men. Psychoneuroendocrinology 23, 45–55.

De Keyser, J., Wilczak, N., Goossens, A., 1994. Insulin-like growth factor-I receptor densities in human frontal cortex and white matter during aging, in Alzheimer's disease, and in Huntington's disease. Neurosci. Lett. 172, 93–96.

Dik, M.G., Pluijm, S.M., Jonker, C., Deeg, D.J., Lomecky, M.Z., Lips, P., 2003. Insulin-like growth factor I (IGF-I) and cognitive decline in older persons. Neurobiol. Aging 24, 573–581.

Dore, S., Kar, S., Quirion, R., 1997. Insulin-like growth factor I protects and rescues hippocampal neurons against beta-amyloid- and human amylin-induced toxicity. Proc. Natl. Acad. Sci. U. S. A. 94, 4772–4777.

Erickson, C.A., Barnes, C.A., 2003. The neurobiology of memory changes in normal aging. Exp. Gerontol. 38, 61–69.

Friedlander, A.L., Butterfield, G.E., Moynihan, S., Grillo, J., Pollack, M., Holloway, L., Friedman, L., Yesavage, J., Matthias, D., Lee, S., Marcus, R., Hoffman, A.R., 2001. One year of insulin-like growth factor I treatment does not affect bone density, body composition, or psychological measures in postmenopausal women. J. Clin. Endocrinol. Metab. 86, 1496–1503.

Han, V.K., 1995. Is the central nervous system a target for growth hormone and insulin-like growth factors? Acta Paediatr. Suppl. 411, 3–8.

Holsboer, F., Oertel, H., Schneider, H.J., Stalla, G.K., Holsboer, F., Zihl, J., 2004. The effect of growth hormone substitution on cognitive performance in adult patients with hypopituitarism. Psychoneuroendocrinology (In press).

Johansson, J.O., Bengtsson, B.A., 1997. Central nervous effects of growth hormone. Endocrinol. Metab. 4 (Suppl. B), 103–107.

Johansson, J.O., Larson, G., Andersson, M., Elmgren, A., Hynsjo, L., Lindahl, A., Lundberg, P.A., Isaksson, O.G., Lindstedt, S., Bengtsson, B.A., 1995. Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters. Neuroendocrinology 61, 57–66.

Kalmijn, S., Janssen, J.A.M.J., Pols, H.A.P., Lamberts, S.W.J., Breteler, M.M.B., 2000. A prospective study on circulating insulin-like growth factor I (IGF-I), IGF-binding proteins, and cognitive function in the elderly. J. Clin. Endocrinol. Metab. 85, 4551–4555.

Kranzler, J.H., Rosenbloom, A.L., Martinez, V., Guevara Aguirre, J., 1998. Normal intelligence with severe insulin-like growth factor I deficiency due to growth hormone receptor deficiency: a controlled study in a genetically homogeneous population. J. Clin. Endocrinol. Metab. 83, 1953–1958.

Lai, Z., Emtner, M., Roos, P., Nyberg, F., 1991. Characterization of putative growth hormone receptors in human choroid plexus. Brain Res. 546, 222–226.

Lai, Z., Roos, P., Zhai, O., Olsson, Y., Fholenhag, K., Larsson, C., Nyberg, F., 1993. Age-related reduction of human growth hormone-binding sites in the human brain. Brain Res. 621, 260–266.

Lamberts, S.W., van den Beld, A.W., van der Lely, A.J., 1997. The endocrinology of aging. Science 278, 419–424.

Laron, Z., Parks, J.S., 1993. Lessons from Laron Syndrome. Karger, Basel.

La Rue, A., 1992. Aging and Neuropsychological Assessment. Plenum Press, New York.

Le Greves, M., Steensland, P., Le Greves, P., Nyberg, F., 2002. Growth hormone induces age-dependent alteration in the expression of hippocampal growth hormone receptor and *N*-methyl-D-aspartate receptor subunits gene transcripts in male rats. Proc. Natl. Acad. Sci. U. S. A 99, 7119–7123.

Lichtenwalner, R.J., Forbes, M.E., Bennett, S.A., Lynch, C.D., Sonntag, W.E., Riddle, D.R., 2001. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience 107, 603–613.

Lijffijt, M., Van Dam, P.S., Kenemans, J.L., Koppeschaar, H.P.F., de Vries, W.R., Drent, M.L., Wittenberg, A., Kemner, C., 2003. Somatotropic-axis deficiency affects brain substrates of selective attention in childhood-onset growth hormone deficient patients. Neurosci. Lett. 353, 123–126.

Lynch, C.D., Lyons, D., Khan, A., Bennett, S.A., Sonntag, W.E., 2001. Insulin-like growth factor-1 selectively increases glucose utilization in brains of aged animals. Endocrinology 142, 506–509.

Markowska, A.L., Mooney, M., Sonntag, W.E., 1998. Insulin-like growth factor-1 ameliorates age-related behavioral deficits. Neuroscience 87, 559–569.

McMorris, F.A., Smith, T.M., DeSalvo, S., Furlanetto, R.W., 1986. Insulin-like growth factor-I/somatomedin C: a potent inducer of oligodendrocyte development. Proc. Natl. Acad. Sci. U. S. A. 83, 822–826.

Morley, J.E., Kaiser, F., Raum, W.J., Perry, H.M., Flood, J.F., Jensen, J., Silver, A.J., Roberts, E., 1997. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. Proc. Natl. Acad. Sci. U. S. A. 94, 7537–7542.

Nilsson, L., Sara, V.R., Nordberg, A., 1988. Insulin-like growth factor 1 stimulates the release of acetylcholine from rat cortical slices. Neurosci. Lett. 88, 221–226.

Nyberg, F., 1997. Aging effects on growth hormone receptor binding in the brain. Exp. Gerontol. 32, 521–528.

Paolisso, G., Ammendola, S., Del Buono, A., Gambardella, A., Riondino, M., Tagliamonte, M.R., Rizzo, M.R., Carella, C., Varricchio, M., 1997. Serum levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 in healthy centenarians: relationship with plasma leptin and lipid concentrations, insulin action, and cognitive function. J. Clin. Endocrinol. Metab. 82, 2204–2209.

Papadakis, M.A., Grady, D., Tierney, M.J., Black, D., Wells, L., Grunfeld, C., 1995. Insulin-like growth factor 1 and functional status in healthy older men. J. Am. Geriatr. Soc. 43, 1350–1355.

Papadakis, M.A., Grady, D., Black, D., Tierney, M.J., Gooding, G.A., Schambelan, M., Grunfeld, C., 1996. Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann. Intern. Med. 124, 708–716.

Peace, K.A., Orme, S.M., Padayatty, S.J., Godfrey, H.P.D., Belchetz, P.E., 1998. Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. Clin. Endocrinol. 49, 391–396.

Poe, B.H., Linville, C., Riddle, D.R., Sonntag, W.E., Brunso-Bechtold, J.K., 2001. Effects of age and insulin-like growth factor-1 on neuron and synapse numbers in area CA3 of hippocampus. Neuroscience 107, 231–238.

Pulford, B.E., Ishii, D.N., 2001. Uptake of circulating insulin-like growth factors (IGFs) into cerebrospinal fluid appears to be independent of the IGF receptors as well as IGF-binding proteins. Endocrinology 142, 213–220.

Pulford, B.E., Whalen, L.R., Ishii, D.N., 1999. Peripherally administered insulin-like growth factor-I preserves hindlimb reflex and spinal cord noradrenergic circuitry following a central nervous system lesion in rats. Exp. Neurol. 159, 114–123.

Rollero, A., Murialdo, G., Fonzi, S., Garrone, S., Gianelli, M.V., Gazzerro, E., Barreca, A., Polleri, A., 1998. Relationship between cognitive function, growth hormone and insulin-like growth factor I plasma levels in aged subjects. Neuropsychobiology 38, 73–79.

Rosenbloom, A.L., Guevara, A.J., Rosenfeld, R.G., Fielder, P.J., 1990. The little women of Loja-growth hormone-receptor deficiency in an inbred population of southern Ecuador. N. Engl. J. Med. 323, 367–374.

Sartorio, A., Molinari, E., Riva, G., Conti, A., Morabito, F., Faglia, G., 1995. Growth hormone treatment in adults with childhood onset growth

hormone deficiency: effects on psychological capabilities. Horm. Res. 44, 6–11.

Sartorio, A., Conti, A., Molinari, E., Riva, G., Morabito, F., Faglia, G., 1996. Growth, growth hormone and cognitive functions. Horm. Res. 45, 23–29.

Scheepens, A., Sirimanne, E.S., Breier, B.H., Clark, R.G., Gluckman, P.D., Williams, C.E., 2001. Growth hormone as a neuronal rescue factor during recovery from CNS injury. Neuroscience 104, 677–687.

Schneider, H.J., Pagotto, U., Stalla, G.K., 2003. Central effects of the somatotropic system. Eur. J. Endocrinol. 147, 377–392.

Soares, C.N., Musolino, N.R., Cunha, N.M., Caires, M.A., Rosenthal, M.C., Camargo, C.P., Bronstein, M.D., 1999. Impact of recombinant human growth hormone (RH-GH) treatment on psychiatric, neuropsychological and clinical profiles of GH deficient adults. A placebo-controlled trial. Arq. Neuro-Psiquiatr. 57, 182–189.

Sonntag, W.E., Lynch, C.D., Bennett, S.A., Khan, A.S., Thornton, P.L., Cooney, P.T., Ingram, R.L., McShane, T., Brunso-Bechtold, J.K., 1999. Alterations in insulin-like growth factor-1 gene and protein expression and type 1 insulin-like growth factor receptors in the brains of ageing rats. Neuroscience 88, 269–279.

Sonntag, W.E., Bennett, S.A., Khan, A.S., Thornton, P.L., Xu, X., Ingram, R.L., Brunso-Bechtold, J.K., 2000a. Age and insulin-like growth factor-1 modulate *N*-methyl-D-aspartate receptor subtype expression in rats. Brain Res. Bull. 51, 331–338.

Sonntag, W.E., Lynch, C., Thornton, P., Khan, A., Bennett, S., Ingram, R., 2000b. The effects of growth hormone and IGF-1 deficiency on cerebrovascular and brain ageing. J. Anat. 197, 575–585.

Stabler, B., Siegel, P.T., Clopper, R.R., 1991. Growth hormone deficiency in children has psychological and educational co-morbidity. Clin. Pediatr. 30, 156–160.

Stenvers, K.L., Lund, P.K., Gallagher, M., 1996. Increased expression of type 1 insulin-like growth factor receptor messenger RNA in rat hippocampal formation is associated with aging and behavioral impairment. Neuroscience 72, 505–518.

Strasburger, C.J., Bidlingmaier, M., Wu, Z., Morrison, K.M., 2001. Normal values of insulin-like growth factor I and their clinical utility in adults. Horm. Res. 55 (Suppl. 2), 100–105.

Van Dam, P.S., Aleman, A., de Vries, W.R., Deijen, J.B., van der Veen, E.A., de Haan, E.H.F., Koppeschaar, H.P.F., 2000. Growth hormone, insulin-like growth factor-I and cognitive function in adults. GH and IGF-I Res. 10, S69–S73.

Van Dam, P.S., Lijffijt, M., De Vries, R., De Winter, C.F., Drent, M.L., Van der Grond, J., Verbaten, M.N., Kenemans, J.L., Aleman, A., de Haan, E.H.F., Koppeschaar, H.P.F., 2002. Cognitive function, selective attention, event-related potentials and ^{1}H magnetic resonance spectroscopy in childhood-onset growth hormone deficiency. Growth Hormone and Growth Factors in Endocrinology and Metabolism Symposium Abstracts, vol. 32. Abstract.

Verhelst, J., Abs, R., 2002. Long-term growth hormone replacement therapy in hypopituitary adults. Drugs 62, 2399–2412.

Vitiello, M.V., Merriam, G.R., Moe, K.E., Drolet, G., Barsness, S., Kletke, M., Schwartz, R.S., 1999. IGF-I correlates with cognitive function in healthy older men and estrogenized women. The Gerontologist 39 (S1), 6 (abstract).

Zhai, Q., Lai, Z., Roos, P., Nyberg, F., 1994. Characterization of growth hormone binding sites in rat brain. Acta Paediatr., Suppl. 406, 92–95.